

Oxaliplatin-induced peripheral neuropathy's effects on health-related quality of life of colorectal cancer survivors

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Abstract Oxaliplatin is a highly neurotoxic chemotherapeutic agent routinely used for the treatment of colorectal cancer. Recent data suggest that oxaliplatin-induced peripheral neuropathy may be long-lasting; however, the effects of persistent neuropathy on colorectal cancer survivors' physical and emotional well-being are not well understood. This cross sectional, descriptive study included persons who had received oxaliplatin-based chemotherapy for treatment of colorectal cancer at Moffitt Cancer Center between 2003 and 2010. Questionnaires including the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool, Center for Epidemiological Studies Depression Scale (CES-D), Insomnia Severity Index, Medical Outcomes Study Short Form 36, and a demographic survey were administered. Pearson's correlations and linear regression analyses were used to examine relationships between neuropathy and depressive symptoms, sleep quality, and health-related quality of life (HRQOL). Eighty-nine percent of participants reported at least one symptom of peripheral neuropathy with a mean of 3.8 (± 2.4) neuropathic symptoms. Depressive

symptoms on the CES-D were significantly associated with more severe peripheral neuropathy ($r=0.38$, $p=0.0001$) and interference with activities ($r=0.59$, $p<0.0001$). Higher degrees of sleep disturbance on the Insomnia Severity Index (ISI) were significantly associated with more severe peripheral neuropathy ($r=0.35$, $p=0.0004$) and interference with activities ($r=0.52$, $p<0.0001$). HRQOL was significantly associated with peripheral neuropathy and interference with activities.

Keywords Oxaliplatin · Oxaliplatin-induced peripheral neuropathy · Colorectal cancer

In the United States, among men and women combined, colorectal cancer is the third leading cause of cancer mortality and accounted for over 51,000 deaths in 2012 [1]. Fortunately, the risk of mortality from colorectal cancer has actually declined over the last 20 years in part, due to early detection and a number of new treatment alternatives such as the chemotherapeutic agent, oxaliplatin [2]. Oxaliplatin was approved by the Food and Drug Administration (FDA) for treatment of metastatic colorectal cancer in 2002 and approved for first-line adjuvant treatment of stage III colorectal cancer in 2004 [2]. The use of oxaliplatin for treatment of colorectal cancer has prolonged the lives of many people diagnosed in later stages of the disease. The most recent statistics indicate a 5-year relative survival rate for colorectal cancer of 64.3 % [3].

Despite its efficacy, there are a number of adverse effects associated with oxaliplatin. In particular, oxaliplatin is highly toxic to the peripheral nervous system and may cause chronic neurotoxicity in up to 50 % of patients [4, 5]. Unlike other neurotoxic chemotherapy drugs, oxaliplatin-induced neurotoxicities may not develop until after completion of chemotherapy and may last for years beyond completion of cancer treatment [6, 7]. Oxaliplatin-induced

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neuropathies are primarily sensory and may include numbness or tingling in the hands or feet, pain or discomfort in the hands or feet, and uncomfortable sensations with exposure to cold temperatures [5, 8–10]. Motor symptoms, which occur less frequently with oxaliplatin, include muscle or joint aches, muscle weakness, and loss of balance [5, 9–11].

Existing data indicate that neurotoxic symptoms negatively impact key elements of quality of life including physical function and emotional well-being in diabetics [12–14] and in oncology patients receiving a variety of neurotoxic chemotherapy drugs [9, 10, 15–18]. Several studies have included colorectal cancer patients treated with oxaliplatin but few have specifically focused on this group [9, 10, 16]. The purpose of this study was to evaluate relationships between neuropathic symptoms, health-related quality of life (HRQOL), depressive symptoms, and sleep in colorectal survivors who were treated with oxaliplatin.

Methods

Participants

Participants were men and women with a history of stage III–IV colorectal cancer treated with oxaliplatin at the Moffitt Cancer Center between 2003 and 2010. Eligibility criteria were that participants: (1) be at least 18 years of age, (2) have been treated with oxaliplatin for stage III–IV colorectal cancer, (3) have no history of cancer other than colorectal cancer, (4) have no preexisting neuropathy before oxaliplatin, (5) have no documented or observable psychiatric or neurologic disorders that would interfere with study participation (e.g., dementia or psychosis), (6) be able to speak and read standard English, and (7) provide written informed consent.

Procedure

The study was approved by the Institutional Review Board at the University of South Florida, and eligible patients were identified through the Moffitt Cancer Center Cancer Registry. Attempts were made to contact all survivors meeting the study criteria by telephone and regular mail. Potential participants were mailed a study packet and a postage-paid return envelope. We attempted to contact a total of 422 potential participants by phone and by mail. A total of 128 survivors, who had all been treated with oxaliplatin, agreed to participate. Of the 128 who agreed to participate, 111 (94 %) survivors completed and returned the study packet. Of the people we were unable to recruit, the primary reasons for not enrolling in the study were lack of ability to contact participants (phone and address changes) and lack of interest (hang ups and nonreturned questionnaires).

Measures

Demographic and clinical data

Demographic data were obtained via a standard self-report questionnaire. Variables assessed were gender, age, race/ethnicity, annual household income, educational level, and marital status. Medical charts for survivors were reviewed at the completion of study participation to obtain information about disease stage and cumulative doses of the chemotherapeutic agent oxaliplatin; however, cumulative dosing information was not available for the majority of participants.

Chemotherapy-induced peripheral neuropathy

Neuropathic symptoms and interference with activities were measured using a modified version of the Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (CIPNAT) consisting of two scales, the symptom experience scale and the interference scale [18]. The symptom experience scale assesses the presence (yes or no), of sensory and motor symptoms on a scale of 0–10 for severity, distress, and frequency for each symptom they affirm as present. The interference scale assesses amount of interference with 13 activities of daily living on a scale of 0 (not interfering at all) to 10 (completely interfering). Scores on the symptom experience scale range from 0 to 248 and scores on the interference scale range from 0–130. Higher scores on the symptom experience scale correspond with more severe CIPN. Higher scores on the symptom interference scale correspond with greater neuropathic interference with usual activities. Correlation with a measure of the same concept ($r=0.83$, $p<0.001$) and differences between contrasting groups ($t=7.66$, $p<0.001$) provide evidence of discriminant validity. High test–retest correlations ($r=0.92$, $p<0.001$), Cronbach's alpha (alpha=0.95), and significant item to total correlations ranging from 0.38 to 0.70 provided evidence of reliability.

Depressive symptoms

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item self-report scale that assesses current depressive symptoms [19]. It is a widely used scale that has proven useful as a screening instrument to detect individuals at risk for depression and to measure depressive symptoms. Cronbach's alphas were 0.85 for the general public and 0.90 for the psychiatric population [20]. Scores range from 0–60 with higher scores indicative of more depressive symptoms. A score of 16 or greater is an indicator of significant depressive symptoms.

Sleep quality

The Insomnia Severity Index (ISI) is a 7-item Likert-type scale that assesses sleep quality [21]. Scores range from 0–28 with higher scores indicating greater sleep disturbance. It has been evaluated for reliability and validity in persons with cancer; internal consistency of 0.74 for the general population and 0.90 for oncology populations have been demonstrated, and test–retest reliability ($r=0.83$) has been demonstrated. Confirmatory factor analysis indicate a two-factor structure and significant correlations with other sleep measures including a sleep diary, polysomnography, and the Dysfunctional Beliefs and Attitudes about Sleep scale indicate construct validity [22].

Health-related quality of life

HRQOL was measured using the Medical Outcomes Study Short Form 36. The SF-36 is a 36-item self-report tool evaluating eight health-related concepts. Alpha coefficients ranged from 0.734–0.813, and discriminate validity has been evaluated [23]. Lower scores indicate worse HRQOL.

Statistical analysis

A priori power analysis indicated that 108 subjects were needed, at 90 % power and 2-sided type I error rate of 0.01, to detect a 10 % or more change in R square (percentage of variation explained) attributed independently to level of neuropathic symptoms. Correlation coefficients, simple regression, and multiple linear regression analysis were used to examine relationships between neuropathy and depressive symptoms, sleep quality, and HRQOL.

Results

Participant characteristics

Table 1 presents the demographic and clinical characteristics of participants. The sample was nearly evenly divided between males and females. The mean age of the sample was 61 years of age (± 11.7) with a range from 25–91 years. Approximately 88 % of the participants were Caucasian, and nearly two thirds were married. With respect to clinical characteristics, 71 % were diagnosed with stage III colorectal cancer. Oxaliplatin-based chemotherapy was initiated at an average of 3 years previously; time since initiation of chemotherapy ranged from 1 to 7 years. We also tried collapsing demographic variables into dichotomous variables, and the results were the same. None of the demographic variables were significantly associated with symptoms of neuropathy.

Peripheral neuropathy

Total scores on the CIPNAT symptom experience scale ranged from 0 to 212 with a mean of 68.7 (± 54.6). Total scores on the interference scale ranged from 0–125 with a mean of 24.9 (± 29.6). The large standard deviations for the CIPNAT symptom experience and interference scales indicate that these variables included a wide range of values. Visual and descriptive analyses of the data did not identify any outliers; nevertheless, we explored the effect of excluding the extreme high and low scores of each outcome variable. This did not change the results.

Eighty-nine percent of survivors reported at least one of nine symptoms of peripheral neuropathy. The mean number of symptoms reported was 3.8 (± 2.4). As shown in Table 2, prevalence rates for peripheral neuropathy symptoms ranged from 34 % for discomfort in hands to 72 % for numbness or tingling in feet. Mean severity by symptom ranged from 4.3 (± 2.8) for trouble with balance to 6.6 (± 2.7) for discomfort in feet. The mean distress scores associated with each symptom ranged from 4.13 (± 3.2) for trouble with balance to 6.24 (± 3.0) for discomfort in feet. The mean frequency, or how often the symptom was experienced, ranged from 4.29 (± 3.1), or about 43 % of the time, for trouble with balance to 8.12 (± 3.0), or about 80 % of the time, for numbness or tingling in feet.

Participants reported that neuropathic symptoms interfered with a variety of activities. The percent of survivors who reported interference with any activity ranged from a low of 24 % who reported that peripheral neuropathy interfered with driving to a high of 60 % who reported that peripheral neuropathy interfered with exercising. Among those who endorsed interference with any activity, the mean rate of interference was ranged from 3.7 (SD=2.7) for writing to 5.3 (± 2.9) for exercising.

Correlates of peripheral neuropathy

By univariate analysis, no demographic variable was significantly associated with the symptom experience scale or the interference scale of the CIPNAT. With respect to clinical variables, there was no association between years since initiation of chemotherapy and the symptom experience scale or interference scale of the CIPNAT. The mean score of the sample on the CES-D was 10.9 (± 10.5). More depressive symptoms on the CES-D were significantly associated with higher scores on the symptom experience scale ($r=0.38$, $p=0.0001$) and with the interference scale ($r=0.59$, $p<0.0001$). The mean score of the sample on the ISI was 7.5 (± 6.3). Higher degrees of sleep disturbance on the ISI were significantly associated with higher symptom experience scale scores ($r=0.35$, $p=0.0004$) and interference scale scores ($r=0.52$, $p<0.0001$).

Table 1 Demographic characteristics ($n=111$)

Variable	Frequency	Percent		
	Male	57	51.4	
	Female	53	47.7	
	Missing	1	0.9	
Race/ethnicity	White/Caucasian	98	88.3	
	Hispanic	7	6.3	
	American Indian/Alaska Native	2	1.8	
	Asian	2	1.8	
	Other or unknown	1	0.9	
	Missing	1	0.9	
	Cancer stage	3 (A, B, or C not documented)	1	0.9
		3A	14	12.6
3B		36	32.4	
3C		28	25.2	
4		32	28.8	
Employment	Full-time	33	29.7	
	Part-time	8	7.2	
	Leave of absence	2	1.8	
	Retired	52	46.8	
	Disabled (collecting Social Security disability)	7	6.3	
	Missing	9	8.1	
Years since oxaliplatin	1	25	22.5	
	2	19	17.1	
	3	23	20.7	
	4	20	18.0	
	5	10	9.0	
	6	7	6.3	
	7	1	0.9	
Marital status	Single, divorced, separated, or widowed	31	27.9	
	Married or partnered	72	64.8	
	Missing	8	7.2	
Income	<50,000/year	45	40.5	
	>50,000/year	40	36.0	
	Missing/prefer not to answer	26	23.4	
Age	Mean/SD	Range		
	61/11.7	25–91		

Relationships of peripheral neuropathy to HRQOL

Scores on the SF-36 subscales are shown in Table 3. Subscale scores were uniformly high and indicative of relatively good quality of life. The lowest subscale score was for general health; this was also the only subscale that was not significantly associated with the symptom experience scale or the symptom interference scale of the CIPNAT. The other seven subscales of the SF-36 were significantly associated with both the symptom experience and the interference scale scores such that worse HRQOL were significantly associated with higher CIPNAT scale scores.

Discussion

Our data demonstrates that colorectal cancer survivors continue to experience oxaliplatin-induced peripheral neuropathy for years following treatment, a finding that was previously described by Park and colleagues [7], who were among the first researchers to empirically challenge the reversibility of oxaliplatin-induced neuropathy and provide objective data of persistent nerve damage in patients 2 years post oxaliplatin treatment. Our findings provide additional data from patients as many as 7 years post oxaliplatin that suggest that neuropathy impacts emotional and physical well-being

Table 2 Means and standard deviation prevalence, severity, distress, and frequency of neuropathic symptoms

Symptom	Prevalence		Severity ^a		Distress ^b		Frequency ^c	
	N	%	Mean	SD	Mean	SD	Mean	SD
1 Numbness or tingling in hands	71	63.96	4.85	2.67	4.59	3.06	7.08	3.40
2 Numbness or tingling in feet	78	70.91	6.17	2.80	5.82	3.17	8.12	2.99
3 Discomfort in hands	37	33.94	5.54	2.76	5.54	2.98	5.92	3.34
4 Discomfort in feet	53	48.62	6.57	2.69	6.24	2.97	8.08	2.77
5 Sensitivity to cold	62	56.36	5.85	2.67	5.77	3.05	6.39	3.08
6 Muscle or joint aches	32	29.36	5.45	2.36	5.09	2.30	6.00	2.89
7 Arms or legs weak	49	45.37	5.04	2.37	4.56	2.53	5.47	3.26
8 Trouble with balance	48	43.64	4.29	2.81	4.13	3.23	4.29	3.06

^a Range=0–10^b Range=0–10 except that 4a=1–10^c Range=0–10 except that 4d=1–10

and HRQOL for years following treatment, affecting ability to carry out usual activities, and contributing to depressive symptoms and sleep disturbance.

While our findings suggest that neuropathy contributes to depressive symptoms, insomnia, and reduced quality of life, the cross sectional design, relatively small sample size, and convenience sampling, limit the generalizability of the study. Persons with a high degree of depressive symptoms and/or insomnia may actually be likely to report more severe neuropathic symptoms and neuropathic interference with activities. Longitudinal studies using larger sample sizes and more diverse racial and ethnic groups are needed to help further define the trajectory of neuropathy over time in this group and identify possible modifiable and nonmodifiable risk factors for severe neuropathy that may influence treatment decisions. Obtaining baseline neuropathy data prior to treatment will be essential as researchers seek to further quantify the trajectory of symptoms and quality of life issues in persons treated with oxaliplatin and also identify predisposing risk factors that may increase the likelihood of developing oxaliplatin-induced peripheral neuropathy.

This study relied on self-reported data and did not include objective measures of nerve function such as neurologic

examination and nerve conduction studies. While objective measures are useful in quantifying the type and severity of nerve damage, they may be of limited use in determining the influence of neuropathy on performance status or quality of life. There remains a lack of consensus among researchers as to the best methods of evaluating neuropathy as an outcome measure [24, 25]; however, numerous studies have demonstrated the reliability and validity of self-report tools for evaluating severity of neuropathic symptoms in patients receiving chemotherapy [18, 25, 26] and self-reported neuropathy has been included as an outcome measure in numerous studies of colorectal cancer patients receiving oxaliplatin-based chemotherapy [27–29]. In order to correlate patient-reported neuropathy with actual nerve function, future studies should incorporate both self-reported and objective data.

We did not identify any demographic characteristics associated with prolonged severe neuropathy. Previous research has identified increasing age as a possible risk factor for peripheral neuropathy [30], although other studies have not demonstrated a relationship between age and neuropathy [31, 32]. Cumulative dose, concurrent treatment with bevacizumab, acute neurotoxicity in a previous cycle, low

Table 3 Correlations between neuropathy symptoms and interference and HRQOL scores from the SF-36

	Mean(SD)	Symptom experiencer	Symptom interfeencer
Physical functioning	73.3 (33.0)	−0.22*	−0.55**
Role emotional	84.8 (24.2)	−0.36**	−0.54***
Role physical	67.5 (31.2)	−0.32**	−0.59***
Bodily pain	68.9 (26.1)	−0.36***	−0.51***
Vitality	58.2 (23.4)	−0.23*	−0.51***
General health	57.1 (10.3)	−0.003	−0.06
Mental health	79.0 (18.9)	−0.26*	−0.43***
Social functioning	78.6 (26.6)	−0.36***	−0.66***

p* values<0.05;*p* values<0.01;****p* values<0.001

body weight, continuous rather than intermittent dosing, and high body surface area have also been identified as potential risk factors for development of chronic neuropathy in persons receiving oxaliplatin [27, 32]. We did not collect data on weight, dosing schedule, body surface area, concurrent bevacizumab, or acute neuropathy from oxaliplatin. Future studies should include these variables because they may significantly influence severity of neuropathic symptoms, especially because dosing and dosing schedule are thought to have more influence on the development of neuropathy than any other factor and recent data indicate that changes in dose schedule from a continuous to intermittent schedule may also improve quality of life [27]. Furthermore, diabetics and people with preexisting neuropathy were excluded from our study but should be included in future studies to further define the role of comorbidities and preexisting neuropathy in the development and progression of oxaliplatin-induced peripheral neuropathy.

We cannot fully explain the lack of relationships between the general health subscale scores and other subscale scores or the relatively low general health scores reported by participants or the relatively low general health scores when compared to the other scores. It may be the result of large variations in some of the demographics. We tried collapsing demographic categories in order to conduct analysis of subgroups, but we were underpowered for this analysis. Future studies should include larger sample sizes and consider subgroup analysis to further define relationships between demographic and clinical data and quality of life, as well as to further delineate the influence of demographic characteristics on health-related quality of life.

Several studies have identified possible genetic risk factors for oxaliplatin-induced peripheral neuropathy, including glutathione S-transferase polymorphisms [33, 34] and variances in the AGXT gene, which is involved in oxalate metabolism [35]. Methodologic issues, such as including participants receiving a variety of neurotoxic chemotherapies, lack of attention to previous history or concurrent risk factors for neuropathy, and lack of inclusion of objective measures of neuropathy, make interpretation of these studies challenging [36]. Although we did not evaluate biomarkers in this study, future studies should evaluate possible genetic factors that could contribute to prolonged severe neuropathy and continue to evaluate possible risk factors, including demographic variables, comorbidities concurrent medications, and dosing schedule, which may be associated with oxaliplatin-induced peripheral neuropathy.

A focus on relieving symptoms and improving physical performance may help improve quality of life and reduce depression in persons suffering from oxaliplatin-induced peripheral neuropathy. Survivorship programs should include systematic assessment for neuropathy, provide rehabilitation when needed, and develop support programs for

colorectal cancer survivors that emphasize the chronic nature of neuropathy, help maximize performance status, and assist patients in adjusting to and coping with physical and role limitations.

Conclusions

Findings from this study suggest that oxaliplatin-induced peripheral neuropathy remains a significant problem for colorectal cancer survivors previously treated with oxaliplatin and is associated with increased depressive symptoms, reduced sleep quality, and reduced HRQOL. Clinicians may wish to incorporate this information into the plan of care of colorectal cancer survivors, enquiring about peripheral neuropathy symptoms and discussing the possible deleterious effects on HRQOL, sleep, and depressive symptoms. Additional research should focus on interventions aimed at alleviating symptoms, improving or maintaining performance status, and helping individuals cope with long-term neurotoxicities associated with oxaliplatin treatment. Additional studies to identify patients at risk of developing severe or permanent neuropathies are also needed.

Conflict of interest The primary author reports no conflict of interest, has full control of all primary data and agrees to allow the journal to review the data if requested.

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