



Impact of oxaliplatin-induced neuropathy in patients with colorectal cancer: a prospective evaluation at a single institution

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ABSTRACT

Oxaliplatin plays a major role in the treatment of colorectal cancer (CRC), but is associated with the development of neuropathies. The main objective of the present prospective study was to estimate the proportion of participants with grade 1, 2, 3, or 4 peripheral sensory neuropathies according to the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events* (version 4) among CRC patients treated with oxaliplatin (adjuvant or metastatic, FOLFOX or XELOX regimens) at the Centre hospitalier universitaire de Sherbrooke. Among the 57 patients so treated between May 2012 and April 2013, about 60% reported grade 2 neuropathy, at maximum, during treatment. About 25% of patients had to stop treatment because of neuropathies. In a subset of patients contacted approximately 22 months after treatment cessation, neuropathies persisted in 70%. Oxaliplatin-induced neuropathy affects a significant number of CRC patients and can influence the course of treatment and outcomes.

Key Words Colorectal cancer, oxaliplatin, neuropathy, chemotherapy-induced peripheral neuropathy

Curr Oncol. 2016 Feb;23(1):e65-e69

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INTRODUCTION

Colorectal cancer (CRC) is one of the three most common cancers in North America¹. Oxaliplatin is frequently used for CRC management in the adjuvant or metastatic setting, and peripheral neuropathy is a dose-limiting effect of that treatment that can persist after cessation of therapy². Previous studies have reported incidences up to 50% for grade 2 or greater neuropathy, and up to 20% for grade 3 or greater neuropathy, but patients with medical conditions or concomitant use of medications that could influence the severity of neuropathy have generally been excluded³⁻⁶.

The incidence and severity of neuropathy, and its impact on the course of treatment, were unknown in our patient population. We therefore conducted this explorative study to describe the occurrence of peripheral sensory neuropathy in oxaliplatin-treated CRC patients at our institution and how it influences the course of treatment.

METHODS

Participants

A prospective study conducted at the Centre hospitalier universitaire de Sherbrooke, an academic tertiary care

centre in Quebec, included patients who had a diagnosis of CRC, were more than 18 years of age, and were newly treated with oxaliplatin regimens such as FOLFOX (fluorouracil-leucovorin-oxaliplatin) or XELOX or CAPOX (capecitabine-oxaliplatin) in the adjuvant or metastatic setting. Patients on a FOLFOX-type⁵⁻⁷ regimen were scheduled to receive, every 2 weeks, intravenous oxaliplatin at an initial dose of 85 mg/m² or 100 mg/m² over 2 hours on day 1, with intravenous leucovorin 400 mg/m² and an intravenous bolus of 5-fluorouracil 400 mg/m² (except for patients on modified FOLFOX7) on day 1, followed by a continuous intravenous 5-fluorouracil infusion over 46 hours for a total of 2400 mg/m² or 3000 mg/m². Patients on a XELOX- or CAPOX-type⁸ regimen were scheduled to receive, every 3 weeks, intravenous oxaliplatin at an initial dose of 130 mg/m² on day 1, plus oral capecitabine 1000 mg/m² twice daily for 14 days. In the adjuvant setting, 12 cycles (about 6 months) were planned at baseline; in the metastatic setting, treatments with oxaliplatin were continued until disease progression or intolerance.

Patients were recruited between May 2012 and April 2013. The treating physician identified eligible patients; those who agreed to meet with the research assistant were invited to participate in the study. The institution's ethics

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committee approved the project, and all participants signed a written consent form.

Objectives

The main objective of the study was to estimate the proportion of CRC patients reporting, at maximum during oxaliplatin treatment, grade 1, 2, 3, or 4 peripheral sensory neuropathies, defined according to the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events* [CTCAE (version 4)]⁹. Those criteria are widely used to study adverse events associated with chemotherapy and to grade their severity. To assess the persistence of peripheral sensory neuropathy, we also contacted, about 24 months after their last treatment, a subset of participants treated in the adjuvant setting who had experienced peripheral neuropathies while on treatment. Secondary objectives were to estimate the cumulative dose of oxaliplatin; the number of cycles received; and the number of patients with oxaliplatin dose reductions, treatment delays, and treatment cessation, all because of neuropathies.

Measures

To screen for the presence of neuropathy, participants completed, with a research assistant at baseline and before each oxaliplatin treatment (maximum follow-up of 12 months on treatment), the Functional Assessment of Cancer Therapy (FACT)/Gynecologic Oncology Group (GOG) neurotoxicity-12 questionnaire (FACT/GOG-Ntx-12, version 4)¹⁰ on peripheral sensory neuropathies. The FACT/GOG-Ntx-12 is a subscale for assessing chemotherapy-induced neurologic symptoms. Its 12 questions (Table 1) assess the presence of sensory symptoms (Ntx 1–4 and Ntx 10), auditory problems (Ntx 6 and 7), motor symptoms (Ntx 5, H12, and An 6), and dysfunction (Ntx 8 and 9) in the preceding 7 days. One question (H12: "I feel weak all over") was excluded from the analysis because it was not specific. Peripheral sensory neuropathy was then graded

by the research assistant according to the CTCAE, with grade 1 being a loss of deep tendon reflexes or paresthesia, but not interfering with function; grade 2 being objective sensory loss or paresthesia interfering with function, but not interfering with activities of daily living; grade 3 being sensory loss or paresthesia interfering with activities of daily living; and grade 4 being permanent sensory loss that interferes with function.

Data collected on patient characteristics included age, sex, CRC treatment [regimen type (FOLFOX or XELOX); cumulative dose of oxaliplatin and number of cycles; number of dose reductions or delays, or treatment cessation because of neuropathy], type of CRC (adjuvant, metastatic, or metastatic resected), and the presence of selected comorbidities (specifically, chronic pain, fibromyalgia, neuropathic pain before oxaliplatin therapy, diabetes, rheumatoid arthritis, multiple sclerosis, chronic renal insufficiency). Furthermore, we determined the use during oxaliplatin therapy of concomitant medications that can influence the level of general pain or neuropathic pain (specifically, acetaminophen, nonsteroidal anti-inflammatory drugs, opioids, topical anesthetics, antidepressants, and anticonvulsants).

Analyses

Based on previous numbers of oxaliplatin-treated CRC patients at our centre (about 96 in 2011), we expected that the study would have to recruit about 75 participants to provide an accurate estimate of the proportion of participants with peripheral sensory neuropathies. Descriptive statistics with proportions were estimated for the maximal grade of sensory peripheral neuropathy and the results from the FACT/GOG-Ntx-12. We also calculated means for cumulative oxaliplatin dose; number of cycles; and dose reductions, treatment delays, and treatment cessations because of chronic peripheral sensory neuropathy. Data for patients who died or were lost to follow-up were included in the analysis.

TABLE 1 Results from the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group neurotoxicity-12 questionnaire^a

Question		Patient responses (%)	
		A little bit or somewhat	Quite a bit or very much
Ntx 1:	I have numbness or tingling in my hands	68.4	10.5
Ntx 2:	I have numbness or tingling in my feet	47.4	1.8
Ntx 3:	I feel discomfort in my hands	57.9	1.8
Ntx 4:	I feel discomfort in my feet	33.3	0
Ntx 5:	I have joint pain or muscle cramps	52.6	3.5
Ntx 6:	I have trouble hearing	26.3	0
Ntx 7:	I get ringing or buzzing in my ears	29.8	0
Ntx 8:	I have trouble buttoning buttons	26.3	0
Ntx 9:	I have trouble feeling the shape of small objects when they are in my hand	35.1	0
An 6:	I have trouble walking	21	3.5
Ntx 10:	I have pain in my hands or feet when I am exposed to cold temperatures	57.9	24.6

^a The proportions of patients who, at least once during follow-up (that is, while on oxaliplatin treatment), reported a "little" or "somewhat," or "quite a bit" or "very much," were combined. Data for patients who reported "not at all" are not shown. Question H12, "I feel weak all over," was excluded from the questionnaire.

RESULTS

Of the 91 patients prescribed oxaliplatin who were screened for eligibility, 34 (37.3%) were excluded (20 had already initiated oxaliplatin, 6 did not have CRC, 3 were participating in another research project, 2 had cognitive problems, and 3 refused to participate). Of the 57 patients enrolled, 5 with metastatic CRC died during follow-up while on treatment; no other participants were lost to follow-up.

Table II outlines the baseline characteristics of the participants and their oxaliplatin treatments. Most participants were prescribed a FOLFOX-type regimen; the stop-and-go approach (that is, cessation of the oxaliplatin-based regimen with gradual reintroduction of the medication^{11,12}) was used in 5 of the 28 patients with metastatic CRC (17.9%). Of the 28 participants with metastatic disease, 18 (64.3%) were treated with oxaliplatin in the first line, and 14 (50%) received bevacizumab in conjunction with oxaliplatin (data not shown). Of the 57 patients overall, 6 (10.5%, 3 in the adjuvant setting) reported grade 1 neuropathy at baseline, and 3 (5.3%, all in the adjuvant setting) reported grade 2 neuropathy at baseline (data not shown).

Table III presents the main study results. Of the overall group, 15 (26%) had 1 or more comorbidities of interest (documented in medical charts or reported by the patients), and 38 (67%) were prescribed 1 or more medications that could influence pain or neuropathy. About 95% reported neuropathies during treatment with oxaliplatin, and nearly 60% had, at maximum, CTCAE grade 2 neuropathies. Table I reports the results from the FACT/GOG-Ntx-12. A high proportion of the participants reported having sensory symptoms during follow-up.

Treatment was stopped prematurely because of neuropathies in 8 of 29 patients on adjuvant therapy (27.6%) and in 6 of 28 patients with metastases (21.4%, including 2 on stop-and-go treatment). In the adjuvant setting, the initially planned 12 cycles were completed for only 6 patients (20.7%). The dose of oxaliplatin was reduced because of neuropathies in 15 of the 57 patients (26.3%): 9 of 29 in the adjuvant group (31%), 5 of 20 in the metastatic not resected group (25%), and 1 of 8 in the metastatic resected group (12.5%). No treatments were delayed because of the presence of neuropathies.

Of the 29 participants treated in the adjuvant setting, 13 (44.8%) agreed to be contacted about 24 months after treatment cessation about the persistence of neuropathies. Of those 13 patients, 1 was lost to follow-up, 1 died, and 1 was excluded from the analysis because he had not reported neuropathies while on treatment. Thus, 10 participants were evaluated for persistent neuropathies about 22 months after oxaliplatin cessation (range: 16–28 months after treatment cessation). Of those 10 patients, 7 (70%) had persistent neuropathies ($n = 4$ grade 1, $n = 2$ grade 2, $n = 1$ grade 3); all but 1 (90%) had a comorbidity that could have influenced the presence of neuropathy; and 4 (40%) were using a medication that could influence the level of pain.

DISCUSSION AND CONCLUSIONS

The present study allowed us to describe our CRC population treated with oxaliplatin and how peripheral sensory

TABLE II Baseline characteristics of the study patients

Characteristic	Value
Patients (<i>n</i>)	57
Age (years)	
Median	66
Range	43–84
Sex [<i>n</i> (%)]	
Men	33 (57.9)
Women	24 (42.1)
White ethnicity [<i>n</i> (%)]	57 (100)
Chemotherapy regimen [<i>n</i> (%)]	
FOLFOX	55 (96.5)
XELOX	2 (3.5)
Type of colorectal cancer [<i>n</i> (%)]	
Adjuvant	29 (50.9)
Metastatic, non-resected	20 (35.1)
Metastatic, resected	8 (14.0)
Patients with comorbidities ^a [<i>n</i> (%)]	15 (26.3)
Chronic pain	9 (15.8)
Type 2 diabetes	6 (10.5)
Chronic renal impairment	3 (5.3)
Rheumatoid arthritis	1 (1.8)
Neuropathic pain	1 (1.8)
Fibromyalgia	0
Multiple sclerosis	0
Concomitant medications ^b [<i>n</i> (%)]	38 (66.7)
Acetaminophen	30 (52.6)
Opioids	15 (26.3)
Antidepressants ^c	8 (14.0)
Anticonvulsants ^d	8 (14.0)
NSAIDs	7 (12.3)
Topic analgesic ^e	5 (8.8)
Cannabinoids ^f	1 (1.8)

- ^a Some patients had more than 1 comorbidity.
 - ^b Some patients took more than 1 medication that could influence pain.
 - ^c Paroxetine, citalopram, mirtazapine, nortriptyline, venlafaxine.
 - ^d Carbamazepine, gabapentin, lamotrigine, pregabalin.
 - ^e Lidocaine, prilocaine.
 - ^f Nabilone.
- FOLFOX = fluorouracil–leucovorin–oxaliplatin; XELOX = capecitabine–oxaliplatin; NSAIDs = nonsteroidal antiinflammatory drugs.

neuropathy influences the course of treatment. Oxaliplatin induced, at maximum, grade 2 peripheral neuropathies in most patients who experienced that side effect while on treatment. Overall, about 77% of the participants experienced sensory peripheral neuropathy of grade 2 or greater ($n = 33$ grade 2, $n = 11$ grade 3), which is higher than expected. In fact, in the MOSAIC trial, grade 2 or greater neuropathy occurred in 44% of participants receiving oxaliplatin (FOLFOX-type regimen for the adjuvant treatment of colon cancer)⁶. Furthermore, in a study of 2710

TABLE III Main results

Variable	Adjuvant	Metastatic		Overall
		Non-resected	Resected	
Patients (n)	29	20	8	57
Cumulative dose (mg/m ²)				
Mean	647.3	671.2 ^a	944.0 ^a	697.3
Range	85–1020	200–1255	595–1110	85–1255
Cycles (n)				
Mean	7.9	7.5	10.8	8.2
Range	1–12	2–15	7–12	1–15
Change in therapy because of neuropathy [n (%)]				
Dose reduction	9 (31.0)	5 (25.0)	1 (12.5)	15 (26.3)
Treatment cessation	8 (27.6)	6 (30.0)	0	14 (24.6)
Worst neuropathy during treatment ^b [n (%)]				
Grade 1	3 (10.3)	4 (20.0)	3 (37.5)	10 (18.2)
Grade 2	18 (62.1)	11 (55.0)	4 (50.0)	33 (57.9)
Grade 3	6 (20.7)	5 (25.0)	0	11 (19.2)

^a At 12 months.

^b Using the U.S. National Cancer Institute's *Common Toxicity Criteria*, version 4. Three patients had no neuropathy, and no grade 4 peripheral sensory neuropathies were reported.

CRC patients treated in the adjuvant setting, the overall rate of grade 2 or greater sensory neuropathy was 43.7% among participants receiving the modified FOLFOX6 regimen and 48.9% among those receiving modified FOLFOX6 plus bevacizumab⁴.

The higher rate of grade 2 or greater sensory peripheral neuropathy observed in our study has several possible explanations. We used a different version of the CTCAE (version 4 vs. versions 1 or 3 in earlier studies), and we included a greater proportion of participants with comorbidities. Most importantly, the CTCAE is often used to grade oxaliplatin-induced peripheral sensory neuropathy, but the interobserver agreement is poor, which could explain variations in the results from our study and others².

The number of participants who could be contacted after treatment cessation was limited, but our results suggest that neuropathies persist for several months after treatment discontinuation. However, most of the contacted patients had a comorbidity that could have contributed to the presence of chronic neuropathy. Similar rates of persistent neuropathy have been reported by other authors, but at different time periods. In the year after treatment completion, maximal grade 2 or greater neuropathies were reported by 26.1% of patients on oxaliplatin and by 32.4% on oxaliplatin with bevacizumab⁴. In the MOSAIC trial, 19.8% of patients reported grade 1 and 3.4% reported grade 2 neuropathy at 18 months⁶.

Our results can also be compared with the findings reported by Park *et al.*¹³, who used the neuropathy sensory subscale of the CTCAE (version 3) to assess oxaliplatin-induced neuropathy on FOLFOX- or XELOX-type regimens in a group of 108 patients with no baseline neuropathy. Their patients received a mean cumulative oxaliplatin dose of 802.8 mg/m², higher than the cumulative dose reached in

our study (697.3 mg/m²). The proportion of their patients who experienced grade 2 neuropathies at maximum was lower than the proportion observed here (41.6% vs. 57.9% in our study); however, more of their patients had grade 3 neuropathies at maximum (29.2% vs. 19.2%). More of their patients also experienced dose reductions (about 30% vs. 26.3% in our study) and premature treatment cessation because of neurotoxicity (33% vs. 24.6%). Most of their patients (79.2% vs. 70% in our study) also reported persistent neuropathic symptoms at long-term follow-up (that is, 29 ± 4 months post-oxaliplatin). Those differences are potentially explained by the higher mean cumulative dose of oxaliplatin received by patients in the Park study, which also included a greater number of participants. Furthermore, as already mentioned, comparison of studies using various versions of the CTCAE grading system can be problematic.

In our study, fewer participants experienced grade 3 neuropathies, which was unexpected considering the inclusion of patients with comorbidities. However, our rate is similar to the 18.2% reported by De Gramont *et al.*⁵ in patients with advanced CRC. The presence of comorbidities in our patient population therefore did not seem to significantly influence the rates of dose reduction and treatment cessation—a finding that supports the hypothesis that comorbidities are not associated with a greater risk of oxaliplatin-induced neuropathy. In fact, earlier trials had not found an association of comorbidities such as diabetes with a greater incidence of oxaliplatin-induced persistent peripheral sensory neuropathy^{14–16}. On the other hand, our lower proportion of participants with grade 3 neuropathy, treatment cessation, and dose reduction might be explained by the inclusion of participants taking pain medications. However, several pharmacologic agents such as antidepressants and antiepileptics have not been

found to significantly reduce the risk of oxaliplatin-induced neurotoxicity¹⁷. Larger studies are needed to elucidate the associations of comorbidities and co-medications with the incidence of peripheral sensory neuropathy.

In our study, a high percentage of patients experienced dose reductions, which can significantly influence the efficacy of treatment and should be taken into account in the process of shared decision-making. Furthermore, many patients treated in the adjuvant setting did not reach the target number of oxaliplatin cycles. Those results highlight the effects of peripheral sensory neuropathy on the course of oxaliplatin treatment.

Our study has several limitations. It included a small number of patients and was conducted at a single centre, which limits generalization of the results. Another limitation is a lack of information about the characteristics of the patients who did not participate. Persistence of neuropathy was assessed only in patients treated in the adjuvant setting; outcomes could be different in the metastatic setting and could be further investigated. We did not compare the occurrence of neuropathies in participants who received oxaliplatin as first- or second-line treatment. Neuropathy was self-reported and not determined by an oncologist's assessment or by nerve-conduction tests. Furthermore, considering the low number of participants, we did not correlate cumulative dose with the reported degree of neuropathy. However, oxaliplatin-induced neuropathy is well known to be dose-related². Our results are limited, but they underline the importance of further studies into various strategies to minimize oxaliplatin-induced neuropathy.

ACKNOWLEDGMENTS

This project was presented at the 2014 annual meeting of the International Society of Oncology Pharmacy Practitioners; Montreal, QC; 2–5 April 2014.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: AB and FL have received speaker fees from Sanofi. The research team received funding from Sanofi for the conduct of this investigator-initiated trial.

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