Original Article

The Incidence of Oxaliplatin-Induced Peripheral Neurotoxicity at Khartoum Oncology Hospital: A Cross-Sectional Survey

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ABSTRACT

Objective: Using oxaliplatin-based chemotherapy in the treatment of cancer patients can cause a unique form of acute and chronic peripheral neurotoxicities. This study mainly aims to assess the incidence of oxaliplatin-induced peripheral neuropathy (OXAIPN). **Methods:** A cross-sectional study among 121 patients treated with oxaliplatin-based chemotherapy was conducted during the period of January to April 2019 at Khartoum Oncology Hospital. The incidence of acute neurotoxicity was assessed using a descriptive questionnaire for most common hyperexcitability and transient symptoms, while the incidence of chronic neurotoxicity was measured by the 20-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for patients with chemotherapy-induced peripheral neuropathy and graded by the National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 4.03. **Results:** Acute and chronic OXAIPN were found in 49.6% and 41.3% of patients, respectively. Most of the patients who developed acute OXAIPN symptoms manifested cold-induced pharyngolaryngeal dysesthesias (73.3%) or perioral paresthesias (71.7%). No significant association exists between the severity of chronic neurotoxicity and basic demographics. Most (79.1%) of the patients did not inform the doctors about their complaints, and 43.5% of those who informed doctors did not take any medication to manage OXAIPN. **Conclusions:** This study exhibits that oxaliplatin-based chemotherapy can cause symptoms of peripheral neurotoxicity in most of the patients with colorectal or gastric cancer in the form of acute neurotoxicity or chronic neurotoxicity.

Key words: Colorectal cancer, gastric cancer, Khartoum Oncology Hospital, oxaliplatin, peripheral neurotoxicity

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Introduction

Oxaliplatin is a third-generation platinum agent that differs in a spectrum of activity from other platinum drugs.[1] It is used with 5-fluorouracil and leucovorin in a combination regimen, known as FOLFOX, or in a combination regimen with capecitabine, known as XELOX, in the treatment of colorectal cancer and pancreatic and gastric malignancies.[2,3] Peripheral neuropathy is one of the major adverse effects of oxaliplatin-based chemotherapy; surely, it is affecting the quality of life of patients. Oxaliplatin-induced peripheral neuropathy (OXAIPN) is exhibited as two particular disorders, producing a unique syndrome of acute neurotoxicity and the chronic one.[4] In acute neurotoxicity, which occurs primarily in most of the patients, the duration of onset starts from minutes to hours from the infusion and usually resolves within a few days. The symptoms of acute neurotoxicity may include paresthesias and dysesthesias in extremities and the perioral area often induced or worsened by cold, muscle cramps, jaw tightness, and spasms in throat muscles.[5] While the symptoms of chronic neurotoxicity include noncold-related dysesthesias and paresthesias of the extremities, these symptoms generally continue among cycles and increase in seriousness with a cumulative dose. The seriousness of the symptoms can affect the daily activities of cancer patients.[5]

Avoidance or lessening of OXAIPN should be a critical objective for the adjustment of the drug regimen. No prophylactic treatment is available for OXAIPN, and interventions are only symptomatic to alleviate the element of neuropathic pain.[2] Several methods to manage OXAIPN have been investigated, and duloxetine is helpful in the management of oxaliplatin-associated neuropathic pain. Other drugs such as gabapentin, lamotrigine, nortriptyline, topical amitriptyline, ketamine, and baclofen, are also shown to be effective.[6] However, an administration of intravenous Ca/Mg does not substantially improve or prevent OXAIPN.[2] Moreover, advising patients to stay away from cold temperatures is essential for the management of OXAIPN. In case patients cannot stay away from cold temperatures, for example, the utilization of refrigerators, they should wear gloves during the exposure. Neuropathy may likewise be decreased by reducing doses and by prolonging the infusion from 2 to 6 h or using a nonpharmacological stop-and-go approach.[2,5]

In Sudan, the incidences of colorectal and gastric cancers are high, and they accounted for approximately 5.4% and 2% of all new cases in 2018, respectively.[7] Although oxaliplatin is used extensively to treat these types of cancers, documented information about OXAIPN in the country appears to be scarce. Thus, conducting this study at Khartoum Oncology Hospital to assess the incidence and severity of acute OXAIPN and oxaliplatin-induced chronic peripheral neuropathy (OXCPN) in oxaliplatin-treated patients will be helpful in early intervention and management.

Methods

Study design

A cross-sectional, hospital-based study was conducted at Khartoum Oncology Hospital, Khartoum, Sudan. The data were collected during the period of January to April 2019.

Patient selection

Patients diagnosed by gastric or colorectal cancers and used oxaliplatin-based chemotherapy (FOLFOX or XELOX) were included in the study; to be eligible for enrollment, patients had to be aged >18 years. Patients with concomitant diseases such as diabetes and liver or renal insufficiency, which would interfere or complicate the clinical assessments, were excluded. At the initial screening stage, a total of 149 patients were scheduled to receive oxaliplatin-based chemotherapy at Khartoum Oncology Hospital, and 28 patients were excluded for various reasons including the presence of diabetes or liver or renal insufficiency (n = 20), change in a treatment plan from oxaliplatin-based chemotherapy to another regimen (n = 7), and refusal to participate (n = 1). All included patients (n = 121) were interviewed, and their medical records were reviewed.

Chemotherapy regimen

For the FOLFOX regimen, oxaliplatin was given at 85 mg/m^2 every 2 weeks for 12 cycles, and for the XELOX regimen, the patients received oxaliplatin at 130 mg/m^2, every 3 weeks for eight cycles. Oxaliplatin was infused intravenously for 2 h for all the patients.

Outcome measures

In acute OXAIPN, 11 of the most common hyperexcitability and transient symptoms were assessed using a simple descriptive questionnaire, which was previously used by Velasco *et al.*, 2014; Argyriou *et al.*, 2013; and Palugulla *et al.*, 2017.[3,8,9] The severity was graded on the basis of the sum of several symptoms: if the patients manifested one to three symptoms, then the severity of OXAIPN was considered to be Grade 1; if the patients showed between four and six symptoms, then the severity of OXAIPN was regarded to be of Grade 2; if the patients exhibited six to nine symptoms, then the severity of OXAIPN was considered to be of Grade 3; and if the patients displayed more than nine symptoms, then the severity of OXAIPN was regarded to be of Grade 4. OXCPN

was assessed using the 20-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for patients with chemotherapy-induced peripheral neuropathy (CIPN), which has sensory, motor, and autonomic neurotoxicity subscales and is considered to be the most widely used cancer-specific quality-of-life questionnaire.[10] The grading was based on the National Cancer Institute's Common Toxicity Criteria, Version 4.03, which is commonly used to monitor and rate the severity of chemotherapy-induced neurotoxicity. A pilot study was conducted, and the chronic questionnaire is shown to be reliable and valid.

Statistical analysis

A descriptive analysis was implemented to examine the main features of the dataset. Descriptive statistics of SPSS provided frequency tables and percentages. Multiple logistic regressions were employed to examine the association between the severity of chronic neurotoxicity induced by oxaliplatin and basic demographics using the International Business Machines, Statistical Package for Social Sciences for Windows, Version 23.0 software (IBM Corp., Armonk, NY, USA).

Ethical considerations

The ethical clearance (FPEC-12-2018) was obtained from the Ethical Committee of the Faculty of Pharmacy, University of Khartoum. Additional approval for checking the medical records was obtained from Khartoum Oncology Hospital. In addition, verbal consent, including a clear explanation of the purpose of the study, was taken from each patient.

Results

A total of 121 patients using oxaliplatin-based chemotherapy were enrolled in this study; 63.6% were males and 36.4% were females. In addition, 44.6% of the patients were 31–50 years old. A total of 75.2% of the patients had colorectal cancer and 24.8% had gastric cancer. Furthermore, 67.8% of the patients were treated with biweekly FOLFOX, and 32.2% of the patients received triweekly XELOX. Regarding the cumulative dose of oxaliplatin, 35.5% of the patients used a cumulative dose of <250 mg/m^2 and 26.4% used a dose of 500–750 mg/m^2. However, 49.6% of the patients developed acute neurotoxicity, and 41.3% of them developed chronic neurotoxicity. Table 1 illustrates the baseline characteristics of the patients.

Table 2 summarizes the incidences of acute neurotoxicity effects secondary to the receipt of oxaliplatin-based chemotherapy. The vast majority of the patients who developed acute neurotoxicity (49.6%) manifested cold-

Table 1: Baseline characteristics of patients using oxaliplatin-based chemotherapy (*n*=121)

Baseline characteristics	*n* (%)
Gender	
Male	77 (63.6)
Female	44 (36.4)
Age group (years)	
18-30	13 (10.7)
31-50	54 (44.6)
51-70	45 (37.2)
>70	9 (7.4)
Tumor type	
Colorectal cancer	91 (75.2)
Gastric cancer	30 (24.8)
Treatment protocol	
FOLFOX	82 (67.8)
XELOX	39 (32.2)
Cumulative dose (mg/m^2)	
<250	43 (35.5)
250-500	25 (20.7)
500-750	23 (26.4)
Type of neurotoxicity	
Acute neurotoxicity (years)	60 (49.6)
18-30	4 (6.7)
31-50	29 (48.3)
51-70	22 (36.7)
>70	5 (8.3)
Chronic neurotoxicity (years)	50 (41.3)
18-30	8 (16)
31-50	21 (42)
51-70	18 (36)
>70	3 (6)
No neurotoxicity (years)	11 (9.1)
18-30	1 (9)
31-50	4 (36.6)
51-70	5 (45.4)
>70	1 (9)
Type of chemotherapy	
Adjuvant	31 (25.6)
Metastasis	90 (74.4)

Table 2: Incidence of acute neurotoxicity symptoms in patients using oxaliplatin-based chemotherapy (*n*=60 of 121 patients; 49.6%)

Symptoms	*n* (%)
Cold-induced perioral paresthesia	43 (71.7)
Cold-induced pharyngolaryngeal dysesthesia	44 (73.3)
Shortness of breath	7 (11.7)
Swallowing difficulty	38 (63.3)
Laryngospasm	36 (60)
Muscle cramp	26 (43.3)
Jaw stiffness	16 (26.7)
Visible fasciculation	10 (16.7)
Voice change	16 (27.7)
Ptosis	5 (8.3)
Visual field change	19 (31.7)

induced pharyngolaryngeal dysesthesias (73.3%) or perioral paresthesia (71.7%). Regarding the grading of acute OXAIPN, the maximum grade was Grade 1 in 25 (41.67%) patients, Grade 2 in 23 (38.33%) patients, and Grade 3 in 12 (20%) patients.

The findings of the study revealed that 41.3% of the patients developed chronic neurotoxicity following the administration of oxaliplatin-based chemotherapy, of whom 72% were treated with FOLFOX [Table 3]. However, 46% of them had cumulative doses of oxaliplatin from 500 mg/m^2 to 750 mg/m^2. A total of 56% of the patients in this study took <6 courses of oxaliplatin-based chemotherapy [Table 3]. The maximum grade of OXCPN was Grade 2 in 21 (42%) patients, Grade 1 in 17 (34%) patients, and Grade 3 in 12 (24%) patients. However, no significant association existed between the severity of OXCPN and chronic baseline characteristics [Table 4].

Regarding the management of OXAIPN, 87 (79.1%) patients did not inform the doctors about their complaints, and only 23 (20.9%) patients informed the doctors about their symptoms. Out of the 20.9% of the patients who informed the doctors, 43.5% have suffered from OXAIPN without intervention. Table 5 depicts the different ways of OXAIPN management including used medications or the reduction of oxaliplatin doses.

Regarding the compliance of patients with the medications, patients who used Vitamin B12 (two patients), gabapentin (two patients), and nonsteroidal anti-inflammatory drugs (NSAIDs) (one patient), we found that 50%, 100%, and 33.3% of the patients were not compliant with their medications, respectively. Moreover, 100% of the symptoms of these patients were not controlled. Patients who used tramadol (2 patients) were compliant with their medications, and their symptoms were controlled. Furthermore, a dose reduction of oxaliplatin (two patients) was effective in controlling the symptoms of OXIPN in 100% of them.

Table 3: Baseline characteristics of patients using oxaliplatin-based chemotherapy and developed chronic neurotoxicity (*n*=50 of 121 patients; 41.3%)

Baseline characteristics	*n* (%)
Gender	
Male	32 (64)
Female	18 (36)
Age group (years)	
18-30	7 (14)
31-50	22 (44)
51-70	18 (36)
>70	3 (6)
Treatment protocol	
FOLFOX	36 (72)
XELOX	14 (28)
Cumulative dose (mg/m^2)	
<250	6 (12)
250-500	23 (46)
500-750	21 (42)
Number of cycles that received	
<6 cycles of treatment	28 (56)
>6 cycles of treatment	22 (44)

Table 4: The association between the severity of oxaliplatin-induced chronic peripheral neurotoxicity and baseline characteristic

Baseline characteristics	Grade of neurotoxicity			*P*
	Grade 1 (*n*=18)	Grade 2 (*n*=19)	Grade 3 (*n*=13)	
Gender				
Male	10	12	10	0.408
Female	8	7	3	
Age group (years)				
18-30	1	5	1	0.310
31-50	10	6	6	
51-70	6	7	5	
>70	1	1	1	
Treatment protocol				
FOLFOX	14	12	10	0.635
XELOX	4	7	3	
Cumulative dose (mg/m^2)				
<250	3	3	0	0.211
250-500	9	11	3	
500-750	6	5	10	
Number of cycles that received				
<6 cycles of treatment	12	14	2	0.123
>6 cycles of treatment	6	5	11	

Discussion

Oxaliplatin-based chemotherapy is the first-line treatment of gastric and colorectal cancers. However, one of the main problems following oxaliplatin administration is the development of acute and chronic peripheral neuropathies,[8] which may often cause chemotherapy discontinuation.[11] Hitherto, efforts to establish a neuroprotective agent against OXAIPN have been unsuccessful, but duloxetine, anticonvulsants, antidepressants, opioids, and topical local anesthetics have been proven effective in diminishing oxaliplatin-associated neuropathic pain.[6] Although OXCPN symptoms are partially resolved in most of the cases, the symptoms may remain for 6–8 months after the discontinuation of oxaliplatin treatment in approximately 40% of the patients,[12] while acute neurotoxicity induced by oxaliplatin is self-limited and reversible in most of the cases in a few days.[13,14]

In this study, the number of male patients (63.6%) is more than that of female patients (36.4%), and this falls within Cancer Statistics 2018 (GLOBOCAN) which showed that

Table 5: Type of therapeutic interventions for patients who informed the doctors about oxaliplatin-induced peripheral neuropathy

Therapeutic interventions	*n* (%)
Medication	
Gabapentin	2 (8.7)
Tramadol	2 (8.7)
NSAIDs	3 (13)
B vitamins	4 (17.4)
Dose reduction	2 (8.7)
Not take any medication	10 (43.5)
Total	23 (100)

NSAIDs: Nonsteroidal anti-inflammatory drugs

colorectal and gastric cancers occur more in males than in females.[15] Furthermore, the colorectal cancer patients were prominent in this study (75.2%), while the percentage of gastric cancer patients was only 24.8%, which is due to the difference in the incidences of colorectal (1398) and gastric (511) cancers in Sudan in 2018.[7] These cancers were mainly treated with the FOLFOX regimen (67.8%), while 32.2% used the XELOX regimen only. The exact explanation for that is the accessibility to patients who used the FOLFOX regimen, and their files are more accessible at Khartoum Oncology Hospital.

In this study, the overall incidence of acute OXAIPN was 49.6%, while the chronic form was 41.3%, and 9.1% did not develop any form of neurotoxicity. For those who developed acute neurotoxicity, 73.3% developed cold-induced pharyngolaryngeal dysesthesias (abnormal or unpleasant sensation of burning or shooting pain that mainly occurred during swallowing) and 71.7% developed perioral paresthesias (abnormal sensation of tingling and numbness in the perioral area). The severity of neurotoxicity was seen more in Grade 1 (41.7%). These findings are in line with the study done by Palugulla *et al.*, where the severity of neurotoxicity was seen more at Grade 1 (64.8%), and the main symptoms manifested in patients were cold-induced pharyngolaryngeal (63.8%) and dysesthesias or perioral (61.1%) paresthesias.[8]

In chronic neurotoxicity induced by oxaliplatin, 72% of the patients were treated by FOLFOX. Actually, the association of the treatment protocol and the increased risk of developing chronic OXAIPN is conflictingly addressed in the literature with reports, suggesting that FOLFOX is associated with an increased incidence of chronic neurotoxicity compared with XELOX,[16,17] whereas others point otherwise.[18,19] However, the cumulative dose of oxaliplatin is the most significantly associated variable that affects chronic OXAIPN, which has shown to be more common at mid-treatment, *i.e.*, the sixth course for FOLFOX and the fourth course for XELOX.[2] In addition, Palugulla *et al.* found that the OXAIPN is prominently at a cumulative dose of >780 mg/m^2.[8] Conversely, 56% of the patients in our study took <6 cycles of oxaliplatin-based chemotherapy [Table 3]. The number of cycles for oxaliplatin-based chemotherapy regimens can affect the incidence of neuropathy.[20]

Grade 2 chronic OXAIPN was seen in 42% of the patients, followed by Grade 1 (34%). Nevertheless, the difference was palpable in the chronic condition between our study and that of Palugulla *et al.*, where the severity of neurotoxicity with Grade 1 is 55.9%, followed by Grade 2 in 42.5% of the patients.[8] The higher incidence of Grade 2 chronic OXAIPN can be explained by the fact that 79.1% of the patients did not inform the doctors about their complaints, which may be due to the perceptions of the patients about the adverse effects of chemotherapeutic agents, as many of them consider that OXAIPN will resolve directly after the completion of treatment. However, out of the 20.9% of the patients who informed the doctors, 43.5% suffered from OXAIPN without intervention. In addition, 17.4% and 13% of the patients used Vitamin B12 and NSAIDs, respectively. Approximately 8.7% of the patients used gabapentin, and the same percentage of patients used tramadol to manage neuropathic pain induced by oxaliplatin. These results show a remarkable difference between prescribed medications and international guidelines that recommended the usage of duloxetine in the management of CIPN at a dose of (60–120 mg/day).[21,22] Nortriptyline, gabapentin, and topical baclofen are also recommended in the management of CIPN,[21] while NSAIDs and acetaminophen have no major role in the management of CIPN.[21] By contrast, B vitamins did not seem to prevent CIPN.[23]

Multiple logistic regressions were used in our study to assess the association between the degrees of the severity of chronic neurotoxicity induced by oxaliplatin and basic demographics and found that no significant association exists between an increase in the severity of chronic neurotoxicity and basic demographics (age, gender, cumulative dose, number of cycles, and treatment protocol). This finding is similar to that of a study done in South Korea.[11] However, Alejandro *et al.* found that the risk of persistent neuropathy increased with a cumulative dose of oxaliplatin and persistent neuropathy in a past cycle.[4]

Because the compliance of patients is one of the most significant components that affect treatment achievement, their noncompliance could have a significant effect on treatment results and direct clinical consequences.[24] Numerous elements may influence treatment compliance, for example, the span of treatment, cost of medicines, adverse effects of drugs, and inappropriate advising and

communication.[24] In this study, 50%, 100%, and 33.3% of the patients who utilized Vitamin B12, gabapentin, and NSAIDs were not compliant with their medications, respectively. Moreover, all the symptoms of these patients were not controlled. Gabapentin was affected by the noncompliance of the patients, although Vitamin B12 and NSAIDs are not proper choices to manage the symptoms of OXAIPN.[21] Conversely, all the patients who utilized tramadol were compliant with the medication, and their symptoms were controlled, which resulted from the appropriate drug and compliance of the patient with the treatment. The patients must be given effective treatments with a reasonable cost and proper counseling, and their awareness of the word significance of utilizing the prescriptions as recommended must be increased to solve the problem of noncompliance after giving them suitable treatments. In addition, reminders and special prescription holders might help in improving compliance.[25]

Finally, the nurses played an essential role in the improvement of awareness about the symptoms and management of chemotherapy-related adverse effects,[26] which substantially could help in the reduction of the side effects and the improvement of the compliance of the patients.[27,28] In this study, although the vast majority of the patients manifested cold-induced pharyngolaryngeal dysesthesia or perioral paresthesia, the nurses advise the patients to avoid being exposed to cold temperatures or to wear gloves during the exposure. Such kind of precautions considered as a nonpharmacological approach to manage these symptoms may assist in the prevention of OXCPN. In addition, the nurses played an essential role in educating the patients about the significance of informing the doctors about the symptoms of OXAIPN to help them in the management of the symptoms.[29] Moreover, the advice of the nurses for the patients about the significance of their compliance with the medications is beneficial to avoid treatment failure.

The main limitation of this study was that the study was cross-sectional; hence, the follow-up for the patients was missing. The follow-up for patients will help to give accurate results and associate the relationship between acute and chronic OXAIPN. Despite these limitations, the findings of this study are novel as they served as the first report about OXAIPN in Sudanese patients. Thus, further studies with a larger Sudanese population, which may include a follow-up for patients, are strongly recommended.

Conclusion

This study demonstrated that the incidences of acute OXAIPN and OXCPN among the cross-sectional samples with gastric and colorectal cancer patients treated at Khartoum Oncology Hospital are 49.6% and 41.3%, respectively. Most (79.1%) of the patients did not inform the doctors about their complaints. Moreover, 43.5% of the patients who informed doctors did not take any medication to manage OXAIPN. Regular assessments for neurotoxicity among patients who use oxaliplatin-based chemotherapy accompanied with the improvement for the awareness of patients toward the symptoms and management of OXAIP are recommended to improve patient outcomes.

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Conflicts of interest

There are no conflicts of interest.

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