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Original Research

Incidence, Severity, and Clinical Correlations of Oxaliplatin- Induced Neuropathy in Patients with Colorectal Cancer: A Single-Institution Experience from Northeast India

Sreya Mallik	Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Assam, India.
Partha Sarathi Roy	Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Assam, India.
Bhargab Jyoti Saikia	Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Assam, India.
Munlima Hazarika	Department of Medical Oncology, Dr. B. Borooah Cancer Institute, Assam, India.
Abhijit Talukdar	Department of Surgical Oncology, Dr. B. Borooah Cancer Institute, Assam, India.

Background and objective: Colorectal cancer is the third most commonly diagnosed cancer worldwide, with increasing incidence in developing countries. Chemotherapy plays a crucial role in the treatment of locally advanced and metastatic colorectal cancer. Oxaliplatin remains a mainstay in the treatment of colorectal carcinoma, but its primary dose-limiting toxicity is neuropathy, which can impact treatment adherence and impair daily living activities. With limited data on the occurrence of oxaliplatin-induced peripheral neuropathy (OIPN) in the Indian population, this study aimed to determine the incidence and severity of oxaliplatin-induced neurotoxicity and its clinical correlations with various parameters in patients with colorectal carcinoma at a cancer care center in Northeast India.

Material and Methods: This prospective observational analysis was conducted on all histologically confirmed cases of colorectal adenocarcinoma who received oxaliplatin-based chemotherapy in an adjuvant or first-line palliative setting at Dr. B. Borooah Cancer Institute between April 2019 and March 2020.

Results: The study evaluated 76 patients with colorectal carcinoma, with a mean age of 54.07 ± 10 years. The majority (65.8%) of patients had adenocarcinoma of the colon, and 34.2% had rectal adenocarcinoma. Twenty-three (30.3%) patients presented with metastatic disease. Oxaliplatin-based chemotherapy regimens included CAPOX (72.4%) and FOLFOX (27.6%). Acute OIPN was observed in 59 patients (77.6%), with the most common symptom being cold-induced perioral paresthesia. The most frequent grade for acute OIPN was grade II (30.3%). Chronic OIPN was observed in 47 (61.8%) patients, with most developing grade II neuropathy, primarily after the fourth cycle of chemotherapy. The incidence of OIPN was higher in patients aged ≥60 years, those receiving a cumulative oxaliplatin dose > 1000 mg/m², and those with baseline low serum magnesium or calcium levels.

Conclusion: Oxaliplatin is a crucial chemotherapy drug used in colorectal cancer, but its significant dose-limiting toxicity is peripheral neuropathy. Early identification of neuropathic symptoms can improve treatment adherence and enhance patients' quality of life.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with 1.9 million new cases and almost 935,000 deaths yearly, according to the World Health Organization GLOBOCAN 2020 database [1]. CRC incidence and mortality rates vary worldwide, increasing mortality in low-resource countries [2]. The incidence of colorectal cancer in India is lower than in Western countries. In India, CRC is the fourth most common cancer in men and the fifth most common in women worldwide [1]. Though the CRC burden is higher in Western countries, the incidence of colorectal cancer also increases in developing countries due to environmental factors and changes in dietary habits and lifestyle.

The choice of therapy for colorectal cancer depends upon the stage of presentation. The Tumour, Node, Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) / Union for International Cancer Control (UICC) is the preferred staging system for CRC [3]. Therapeutic management of CRC is challenging and depends on the disease stage of diagnosis. Surgical resection is the only curative modality of treatment for early and localized colorectal cancer (stage I to III). More than 50% of patients either have metastases at the time of presentation or develop during the disease [4].

Chemotherapy plays a significant role in the treatment of locally advanced resected colorectal cancer and metastatic colorectal cancer. 5-fluorouracil (5-FU) has been the mainstay in treating advanced colorectal cancer since the late 1950s [5]. Later on, oxaliplatin was combined with 5-FU/LV chemotherapy, and it demonstrated prolonged disease-free progression and overall survival [6]. In adjuvant and palliative settings, the recommended first-line chemotherapy regimen consists of oxaliplatin-based doublet or triplet drugs [7].

Oxaliplatin is a third-generation platinum compound (1-2, di-amino cyclohexane oxalate platinum) which is a non-specific cell cycle agent with activity in all phases of the cell cycle. It covalently binds to the N7 position of guanine and adenine to form a DNA adduct and results in the inhibition of DNA synthesis and function. Oxaliplatin has remained the backbone in treating colorectal carcinoma, both locally advanced and metastatic disease [8]. However, its anti-cancer efficacy is associated with adverse reactions like nausea and vomiting, diarrhoea, mouth sores, myelosuppression, fatigue, and chemotherapy-induced peripheral neuropathy (CIPN), the main dose-limiting toxicity [9].

The side effects of oxaliplatin infusion can limit patient compliance during cancer treatment. Oxaliplatin is one of the most neurotoxic anti-cancer drugs, alongside vinca-alkaloids, taxanes, bortezomib, and thalidomide [10]. Oxaliplatin induces acute and transient nerve hyper- excitability followed by chronic cumulative peripheral neuropathy [10]. Chemotherapy-induced peripheral neuropathy is usually related to cumulative dose or dose intensity. The neurotoxicity seen with oxaliplatin can manifest as two distinct syndromes: a transient, acute syndrome that can appear during or shortly after infusion and a dose-limiting, cumulative sensory neuropathy. More than 90% of patients experience acute symptoms resolved within a few days, and 30–50% suffer from chronic oxaliplatin-induced peripheral neuropathy (OIPN) [11]. OIPN can experience sensory and motor symptoms, which can cause problems with regular daily activities, necessitating dose reduction. OIPN may be aggravated by pre-existing neurological disorders, diabetes mellitus, advanced age, poor performance status, and dyselectrolytaemia [12].

Considering the rising incidence of advanced colorectal cancer in India and the increasing use of oxaliplatin-based chemotherapy regimens, a proper understanding of OIPN is required. As in the Indian scenario, the patients' overall performance status and nutritional condition are below the expected standard, and it is difficult to balance the associated complications that may arise due to chemotherapy with the efficacy of therapy. There is a lack of Indian data regarding the occurrence of chemotherapy-induced neuropathy.

This prospective study is designed to establish the incidence and severity of oxaliplatin-induced neurotoxicity and its clinical correlation with various clinical and biochemical factors in patients with colorectal cancer treated in tertiary cancer care centres in North-East India.

Materials and Methods

A prospective observational single institutional study was performed on all histologically confirmed cases of colorectal adenocarcinoma who received oxaliplatin-based chemotherapy either in the adjuvant setting or first-line palliative setting at the Department of Medical Oncology, Dr. B. Borooah Cancer Institute (BBCI) during the period from April 2019 to March 2020.

Inclusion criteria: Adult patients (≥18 and <70 years) with stage IIA (high-risk), stage IIB, stage III, and stage IV colorectal adenocarcinoma, ECOG performance status 0-2, having a life expectancy ≥6 months with normal liver, renal function.

Exclusion criteria: Age <18 years or ≥70 years, ECOG performance score >2, diabetes mellitus, renal insufficiency, or any other condition or medication that could interfere or complicate the clinical assessment, pre-existing neurological disorder at baseline screening, previously having a history of receiving any chemotherapy or radiotherapy due to other malignancy.

All the patients reporting to Dr. B. Borooah Cancer Institute fulfilling the inclusion criteria for the duration of one year (April 2019 to March 2020) are included in the study, and clinical data are obtained by clinical evaluation of the patients and also by reviewing patient's files/charts/ reports and Hospital medical records. Patients fulfilling the inclusion criteria were followed prospectively for developing oxaliplatin-induced peripheral neuropathy (OIPN) and severity of neuropathy.

The oxaliplatin-based chemotherapy was either 'FOLFOX-6' or 'CAPOX' regimens in the adjuvant or first-line palliative settings. CAPOX regimen consisted of oxaliplatin 130 mg/m² on day1 as a two-hour infusion and capecitabine 1000 mg/m² per oral twice daily from day1 to day14. The chemotherapy cycle was repeated every 3 weeks for 6-8 cycles. FOLFOX-6 regimen was administered consisting of leucovorin 400 mg/m² as a 2-hour infusion on day1, followed by 5-fluorouracil 400 mg/m² on day1 as an intravenous bolus followed by 5-fluorouracil 2400 mg/m² as a continuous infusion for 46 hours and oxaliplatin 100 mg/m² was given as a 2-hour intravenous infusion concurrent with leucovorin on day1. The chemotherapy cycle was repeated every 2 weeks for 12 cycles.

The severity of oxaliplatin-induced neuropathy was evaluated at baseline, during each chemotherapy cycle, and every two months after treatment completion until one year after starting chemotherapy. The severity of cumulative OIPN was graded using version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAEv5.0) [13] for sensory and motor neuropathy. A descriptive questionnaire assessed the frequency of the common hyperexcitability symptoms associated with acute OIPN.

Dose adjustments of oxaliplatin or treatment delays were calculated according to toxicity grade. Dose modifications were determined according to the most significant degree of toxicity.

The occurrence or presence of acute neuropathy was defined as any episode of acute neurologic symptoms developed during chemotherapy.

The occurrence of chronic neuropathy was defined by the development of any symptoms related to chronic cumulative Neuropathy during the entire course of chemotherapy.

The effect of various clinico-demographic and biochemical parameters on neurotoxicity was

evaluated during therapy. Complete hemograms, liver function tests, and renal function tests were done before every cycle. Blood samples for serum albumin, serum magnesium, and serum calcium were obtained before initiation of chemotherapy and during each chemotherapy cycle. Various clinico-demographic parameters and baseline values of serum magnesium, serum calcium, and serum albumin were correlated with oxaliplatin-induced neuropathy.

Statistical Methods: Statistical analyses were performed using SPSS® for Windows®, version 21.0 (SPSS Inc., Chicago, IL). Descriptive statistics were reported as percentage, mean, standard deviation, and median values. Data were expressed with frequency distribution and rates. Chi-square or Fisher's exact test evaluates the association between categorical variables. Binary logistic regression is used to assess the odds ratio to find out the possible risk of developing an event. A two-tailed $p < 0.05$ was considered statistically significant at a 5% significance level.

Results

Between April 2019 and March 2020, 153 patients with colorectal carcinoma were planned for chemotherapy. Among these patients, 114 were scheduled for oxaliplatin- based chemotherapy either in the adjuvant or first-line palliative setting. A total of 97 patients fulfilled the inclusion criteria. Of these 97 patients, 21 patients defaulted during chemotherapy. Altogether, seventy-six patients were finally included in the analysis.

Baseline Characteristics

A. Demography

The median age of presentation was 54.07 years. Twenty-nine patients (38.25%) were aged more than 60 years. Fifty-four patients (71.1%) were male, with a male- to-female ratio of 2.5:1. More than half had a performance status of ECOG 1. Twenty-six patients (34.2%) had a smoking history, and 31 (40.8%) had a history of alcohol consumption. Forty-six (60%) patients were from rural backgrounds. Further details about the demographic characteristics are described in the Table 1.

Characteristics (N=76)	No. of Patients (%)
Age in years	
Mean ± SD, Range; Median	54.07 ± 10, 29 – 69; 55
Gender	
Male	54 (71.1)
Female	22 (28.9)
ECOG Performance status	
0	9 (11)
1	42 (56)
2	25 (33)
History of Smoking	
Yes	26 (34.2)
No	50 (65.8)
History of Alcoholism	
Yes	31 (40.8)
No	45 (59.2)
Residence	
Rural	46 (60.1)
Urban	30 (39.1)

Table 1. Demography.

B. Clinical Characteristics

Fifty patients (n=50/76, 65.8%) had histologically proven colon adenocarcinoma; the rest had rectal adenocarcinoma (n=26/76; 34.2%). Forty-four (57.9%) patients presented with TNM stage III, followed by 30.3% with stage IV, and only 11.8% with stage II disease.

The median serum calcium level was 9.5 mg/dl (range: 7.9 - 10.9 mg/dl), and the median serum magnesium level was 1.85 mg/dl (range: 1.5 - 2.3 mg/dl). At baseline, fifteen patients (n=15/76, 19.7%) had low serum calcium levels (defined as serum calcium level less than 8.8 mg/dl; per institutional laboratory value). Twenty-four (n=24/76, 31.6%) patients had low serum albumin levels before starting chemotherapy (serum albumin level <3.5 gm/dl; as per institutional laboratory value). Thirty patients (39.5%) had baseline anaemia (haemoglobin less than 12 g/dl). Thirty-six patients (n=36/76, 47.4%) had hypomagnesemia at baseline (defined as serum magnesium level <1.8 mg/dl; as per institutional laboratory value). The detail of clinical characteristics is demonstrated in Table 2.

Characteristics (N= 76)	No. of Patients (%)
Primary disease site	
Colon	50 (65.8)
Rectum	26 (34.2)
TNM Stage	
II	9 (11.8)
III	44 (57.9)
IV	23 (30.3)
Baseline Serum Calcium	
Low	15 (19.7)
Normal	61 (80.3)
Baseline Serum Magnesium	
Low	36 (47.4)
Normal	40 (52.6)
Baseline Haemoglobin	
Low	30 (39.5)
Normal	46 (60.5)
Baseline Albumin	
Low	24 (31.6)
Normal	52 (68.4)

Table 2. Clinical Characteristics.

C. Treatment Characteristics

All the patients in this study received chemotherapy either with the ‘FOLFOX-6’ or ‘CAPOX’ regimen. Forty-eight patients (63.2%) received chemotherapy as part of adjuvant therapy, and 28 patients (36.8%) received palliative chemotherapy. Fifty-five patients (72.4%) received the ‘CAPOX’ regimen, and 21 (27.6%) received the ‘FOLFOX-6’ regimen. Details of treatment characteristics are shown in Table 3.

Characteristics (N=76)	No. of Patients (%)
Intent of Chemotherapy	
Curative	48 (63.2)
Palliative	28 (36.8)
Chemotherapy Regimen	
FOLFOX-6	21 (27.6)
CAPOX	55 (72.4)

No Chemotherapy Cycles	
Mean ± SD, Range	8.91 ± 2, 6 – 12
Cumulative dose of Oxaliplatin (mg/m²)	
Mean ± SD, Range; Median	1057.8 ± 74.6, 780 – 1200; 1040

Table 3. Treatment Characteristics.

Acute Oxaliplatin-induced Peripheral Neuropathy (acute OIPN): Severity

Our study observed Acute OIPN in 59 patients (n=59/76, 77.6%). Forty-four patients (n=44/50, 88%) of colon carcinoma developed acute OIPN, whereas 15 patients (n=15/26, 57.7%) of rectal carcinoma developed acute neuropathy.

The median number of symptoms was 3 (range, 1 - 6) in patients who developed acute OIPN. Most patients had cold-induced perioral paresthesia (88.5%) or pharyngo-laryngeal dysesthesias (85.1%) as the manifestations of acute OIPN. Different presentations (symptoms) of acute neuropathy are described in Table 4.

Symptoms	No. of Patients, n (%)
Cold-induced perioral paresthesia	52 (88.5)
Cold-induced pharyngo-laryngeal dysesthesias	50 (85.1)
Shortness of breath	12 (21)
Difficulty in swallowing	15 (26.3)
Laryngospasm	1 (1.7)
Muscle cramps	23 (39.2)
Jaw stiffness	20 (34.5)
Visible fasciculation	6 (10.5)
Voice change	2 (3.3)
Ptosis	0
Ocular changes	0

Table 4. Incidence of Acute Neuropathic Symptoms.

Acute Oxaliplatin-induced Peripheral Neuropathy (acute OIPN): Severity

Out of 59 patients who developed acute neuropathy, most developed grade II neuropathy. The Acute oxaliplatin-induced peripheral neuropathy was graded as I in 19 patients (25%), grade II in 23 patients (30.3%), and grade III in 17(22.4%) patients. None was diagnosed to have grade IV acute neuropathy.

Chronic Oxaliplatin-induced Peripheral Neuropathy (chronic OIPN): Incidence

Oxaliplatin-induced chronic cumulative neuropathy was developed in 47 patients (n=47/76, 61.8%). Among 47 patients who developed chronic OIPN, 41 (n=41/47, 87.2 %) had any form of acute OIPN during their chemotherapy. Most patients who developed chronic cumulative neuropathy had one or more episodes of acute OIPN. Association of chronic neuropathy and acute neuropathy is shown in Table 5.

		Chronic Neuropathy (n, %)		Total (n, %)

		No	Yes	
	No	11	6	17
Acute neuropathy		64.70%	35.30%	100.00%
	Yes	18	41	59
		30.50%	69.50%	100.00%
Total		29	47	76
		38.20%	61.80%	100.00%

Table 5. Association of Chronic Neuropathy and Acute Neuropathy.

Chronic Oxaliplatin-induced Peripheral Neuropathy (chronic OIPN): Severity

Most of the patients with chronic neuropathy had grade II neuropathy. The Chronic oxaliplatin-induced peripheral neuropathy was graded as I in 15 patients (19.7%), grade II in 21 patients (27.6%), and grade III in 11(14.5%) patients. One patient (1.3%) developed grade IV chronic neuropathy.

Most patients (n=36/47; 76.5%) started to manifest symptoms/signs of chronic OIPN after 4^{th} cycle of chemotherapy.

Twelve patients (15.7%) required the infusion of oxaliplatin over more than two hours because of the severity of their acute OIPN. Seven patients (9.2%) out of 76 needed dose reduction due to the development of grade III neuropathy. One of these seven patients required permanent chemotherapy discontinuation after the 7^{th} cycle due to grade IV neuropathy.

Association of clinical and biochemical parameters with oxaliplatin-induced Neuropathy

In multivariate analysis, it has been seen that acute and chronic OIPN occurrence was correlated with various clinico-pathological and biochemical parameters.

A. Association of clinicopathological variables and Acute OIPN

In this study, acute OIPN was observed more in patients with advanced age (aged ≥60 years). The development of acute OIPN was also high in patients who received cumulative oxaliplatin doses of >1000 mg/m^2, which is statistically significant. The baseline low serum magnesium level was also significantly correlated with acute OIPN. Gender, smoking & alcohol history, chemotherapy regimen, and baseline low hemoglobin & calcium levels did not seem to be associated with the development of clinically significant acute OIPN. Further details of association between acute neuropathy and clinical variables are described in Table 6.

	Acute Neuropathy (n, %)				
		No	Yes	Total	P value
Gender	Male	5 (22.7)	17 (77.3)	22 (100)	
	Female	12 (22.2)	42 (77.8)	54 (100)	0.962
	Total	17 (22.4)	59 (77.6)	76 (100)	
Age (years)	<60	16 (34)	31(66)	47 (100)	
	≥60	1 (3.4)	28 (96.6)	29 (100)	0.02
	Total	17 (22.4)	59 (77.6)	76 (100)	
Chemotherapy regimen	FOLFOX-6	4 (19)	17 (81)	21 (100)	
	CAPOX	13 (23.6)	42 (76.4)	55 (100)	0.668

	Total	17 (22.4)	59 (77.6)	76 (100)	
History of smoking	No	13 (26)	37 (74)	50 (100)	
	Yes	4 (15.4)	22 (84.6)	26 (100)	0.292
	Total	17 (22.4)	59 (77.6)	76 (100)	
History of alcohol intake	No	10 (22.2)	35 (77.8)	45 (100)	0.971
	Yes	7 (22.6)	24 (77.4)	31 (100)	
	Total	17 (22.4)	59 (77.6)	76 (100)	
Total cumulative oxaliplatin dose (mg/m²)	<1000	5 (62.5)	3 (37.5)	8 (100)	0.004
	≥1000	12 (17.6)	56 (82.4)	68 (100)	
	Total	17 (22.4)	59 (77.6)	76 (100)	
Baseline calcium level	Normal	16 (26.2)	45 (73.8)	61 (100)	
	Low	1 (6.7)	14 (93.3)	15 (100)	0.103
	Total	17 (22.4)	59 (77.6)	76 (100)	
Baseline hemoglobin level	Normal	11 (23.9)	35 (76.1)	46 (100)	0.689
	Low	6 (20)	24 (80)	30 (100)	
	Total	17 (22.4)	59 (77.6)	76 (100)	
Baseline magnesium level	Normal	16 (40)	24 (60)	40 (100)	<0.0001
	Low	1 (2.8)	35 (97.2)	36 (100)	
	Total	17 (22.4)	59 (77.6)	76 (100)	

Table 6. Association of Acute Neuropathy with Clinical Variables.

B. Association of clinicopathological variables and Chronic OIPN

This study observed chronic OIPN in patients aged ≥60 years, similar to acute OIPN. There is also a statistically significant correlation between the development of chronic OIPN and cumulative dose of oxaliplatin of >1000 mg/m² and baseline low serum calcium level. The associations between clinicopathological variables and chronic neuropathy are shown in Table 7.

	Chronic Neuropathy (n, %)				
		No	Yes	Total	p-value
Gender	Female	5 (22.7)	17 (77.3)	22 (100)	0.077
	Male	24 (44.4)	30 (55.6)	54 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Age (years)	<60	22 (46.8)	25 (53.2)	47 (100)	0.048
	≥60	7 (24.1)	22 (75.9)	29 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Chemotherapy	FOLFOX-6	7 (33.3)	14 (66.7)	21 (100)	0.593
regimen	CAPOX	22 (40)	33 (60)	55 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
History of smoking	No	19 (38)	31 (62)	50 (100)	0.969
	Yes	10 (38.5)	16 (61.5)	26 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
History of alcohol intake	No	14 (31.1)	31 (68.9)	45 (100)	0.128
	Yes	15 (48.4)	16 (51.6)	31 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Total cumulative	<1000	6 (75)	2 (25)	8 (100)	0.023

oxaliplatin dose (mg/m²)					
	≥1000	23 (33.8)	45 (66.2)	68 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Baseline calcium level	Normal	27 (44.3)	34 (55.7)	61 (100)	0.027
	Low	2 (13.3)	13 (86.7)	15 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Baseline hemoglobin level	Normal	19 (41.3)	27 (58.7)	46 (100)	0.484
	Low	10 (33.3)	20 (66.7)	30 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Baseline magnesium level	Normal	16 (40)	24 (60)	40 (100)	0.727
	Low	13 (36.1)	23 (63.9)	36 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	
Baseline albumin level	Normal	21 (40.4)	31 (59.6)	52 (100)	0.556
	Low	8 (33.3)	16 (66.7)	24 (100)	
	Total	29 (38.2)	47 (61.8)	76 (100)	

Table 7. Association of Chronic Neuropathy with Clinical Variables.

Discussion

Colorectal cancer has become a significant burden in developing countries in the last decade. Majority of the patients present with locally advanced or metastatic disease. Chemotherapy plays a substantial role in the treatment of colorectal cancer. Oxaliplatin is commonly incorporated in the standard therapy of colorectal cancer both in adjuvant and palliative settings. Oxaliplatin, a third-generation platinum compound, can induce two clinically distinct forms of peripheral neuropathy, acute and chronic, through different mechanisms. The oxaliplatin-induced peripheral neuropathy can decrease not only the quality of life of patients but also cause dose reduction and even treatment interruption. Acute OIPN is reversible, but chronic OIPN is often dose-limiting and long-lasting. However, acute neurotoxicity is related to the onset and severity of chronic neuropathy.

A total of seventy-six patients were analysed in the study who received chemotherapy during the study period. The median age of the study population was 55 years, with male to female ratio of 2.5:1. Majority (65.8%) of the patients had adenocarcinoma of the colon. Fifty-five patients (77.2%) received the ‘CAPOX’ regimen; the rest got the ‘FOLFOX-6’ regimen. The median number of chemotherapy cycles received was 8 (range 6-12).

Oxaliplatin induces both reversible acute and partially irreversible cumulative neuropathy. We observed acute OIPN in 59 out of 76 patients and chronic OIPN in 47 out of 76. Acute OIPN and chronic OIPN incidences were 77.6% and 61.8%, respectively. Storey DJ et al. [14] also reported a similar incidence of oxaliplatin-induced Neuropathy in their study. The symptoms of acute neurotoxicity are different from those of chronic neurotoxicity. In our study, most patients experienced cold-induced perioral (88.5%) or pharyngo-laryngeal dysesthesias (85.1%). There is evidence that cold exposure can further affect sodium channel kinetics, thus predisposing to ectopic activity [15]. Such symptoms may result from an acute, abnormal, oxaliplatin-induced hyperexcitability state of peripheral sensory and motor nerve fibres, including those of the cranial nerves [16]. The majority of the patients developed grade II acute neuropathy, followed by grade I and grade III. Among 47 patients who developed chronic OIPN, 41 (87.2%) had acute OIPN symptoms during their previous chemotherapy cycle. These results are similar to a study conducted by Andreas A. Argyriou et al. [17], who also reported that most patients who developed chronic cumulative neuropathy had one or more episodes of acute OIPN. Our study also suggests that acute

OIPN may predispose patients to the chronic, cumulative form. In this study, seven patients (9.2%) out of 76 needed dose reduction due to the development of grade III neuropathy, and one patient required permanent discontinuation of chemotherapy due to grade IV neuropathy. Twelve patients (15.7%) required prolonged infusion of oxaliplatin infusion due to acute neuropathy. This rate is similar to the rate observed in other studies [18].

The incidence of acute OIPN is higher in the elderly than younger population (96.6% vs. 66% in patients aged ≥60 years vs. <60 years, respectively). Advanced age significantly correlated with the development of acute OIPN with a p=0.002. Bandos et al. [19] also suggested that older adults developed more neuropathy than younger adults. The association between the development of acute OIPN and chemotherapy regimen (FOLFOX vs. CAPOX), the intent of chemotherapy, smoking, or alcohol history also failed to reach the significance in this study. Jinrui Li et al. [20] also failed to observe a similar association in their study. However, the occurrence of acute OIPN was related to the cumulative dose of oxaliplatin. Patients who received cumulative oxaliplatin dose >1000 mg/m² had a higher incidence of acute OIPN than those who received cumulative oxaliplatin dose <1000 mg/m² (p=0.004). This finding is supported by a study (Argyriou AA et al.) [17] where cumulative oxaliplatin dose was associated with acute and chronic OIPN development. Acute oxaliplatin- induced peripheral neuropathy is caused by a nodal axonal voltage-gated channel dysfunction resulting in interference with channel kinetics, reducing the overall sodium current. Magnesium modulates vasomotor tone, peripheral blood flow, and blood pressure and exerts several beneficial effects on vascular endothelium and function [21]. Amighi J et al. [22] reported that low serum magnesium concentration may be associated with neurological disease. In the present study, baseline low serum magnesium value significantly correlates with the development of acute OIPN (p=<0.001). The logistic regression analysis indicated that baseline low serum magnesium concentration is an independent predictor of the development of acute OIPN. But baseline serum calcium level, serum albumin level, and presence of anaemia are not significantly associated with the development of acute OIPN. Jinrui Li et al. [20] also found that lower serum magnesium concentration was related to a higher risk of acute oxaliplatin-induced peripheral neuropathy.

Chronic OIPN was also found to occur more in the older population (>60 years of age) with a statistical significance (p=0.048). Similarly, the other demographic parameters like gender, smoking history, and alcoholism failed to reach the importance of developing chronic OIPN. However, the occurrence of chronic OIPN was also related to the cumulative dose of oxaliplatin. Patients who received a cumulative oxaliplatin dose of >1000 mg/m²developed chronic OIPN more than those who received <1000 mg/ m² (p=0.023). De Gramont et al. [23] showed that the risk of permanent neuropathy significantly increases at cumulative oxaliplatin doses above 1,000 mg/m². Ahmed Gaballah et al. [24] found that 29% of the study population developed grade II-III neuropathy with a mean cumulative dose of 850 mg/m². A possible pathogenic hypothesis is that, in addition to the decreased cellular metabolism and axoplasmic transport in dorsal root ganglionic cells, the prolonged activation of voltage-gated sodium channels may induce cellular stress, further affecting the sensory nerve cells and contributing to the development of chronic OIPN. In most patients in our study, cumulative neurotoxicity was observed after a median of four cycles of oxaliplatin-based chemotherapy. Similar results were seen in other studies, where dose-limiting neuropathy was observed in 20% of the patients after 6-cycles, 38% after 9-cycles, and 63% after 12-cycles [25, 26]. Baseline low serum calcium value significantly correlates with our study's development of chronic OIPN (p=0.027). The logistic regression analysis indicated that baseline low serum calcium concentration is an independent predictor of the development of acute OIPN. But baseline serum magnesium level, serum albumin level, and presence of anaemia are not significantly related to the development of chronic OIPN. Several studies showed infusion of calcium and magnesium reduces the severity of neuropathy [27].

Several studies are on the way to discovering the exact mechanism of OIPN and the drugs to interfere with the pathogenesis of OIPN. Oncologists should be alert and aware of the neuropathy arising from oxaliplatin use. And they should take proper preventive measures to reduce the

intensity of acute OIPN because acute hyperexcitability syndrome may strongly predict the development of chronic disabling neuropathy.

In conclusion, Oxaliplatin is one of the significant chemotherapeutic agents in treating colorectal carcinoma. But the major limitation of oxaliplatin use is the dose- limiting neuropathy which can interfere with quality of life. This study demonstrates that most patients with colorectal carcinoma, who received oxaliplatin- based chemotherapy, manifested a transient, acute hyperexcitability syndrome that may contribute to the development of chronic peripheral neuropathy. There is no data to guide any pharmacological therapy to prevent oxaliplatin-induced neuropathy. Identifying patients at high risk of developing acute oxaliplatin-induced peripheral neuropathy is essential. Prospective studies with large population sizes are still needed to establish the predictive factors for the development of neuropathy.

Acknowledgments

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Compliance with Ethical Standards

The study was approved by the Institutional Ethics Committee at the Dr B Borooah Cancer Institute, Guwahati, India.

Conflict of Interest

Authors declare no conflict of interest.

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