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COMPARATIVE STUDY OF PERIPHERAL NEUROPATHY AMONG COLORECTAL CANCER PATIENTS RECEIVING FOLFOX-4 AND XELOX

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ABSTRACT

Background: Oxaliplatin, in combination with 5-fluorouracil (FOLFOX) or capecitabine (XELOX), is standard in colorectal cancer treatment but is associated with peripheral neuropathy (OXA-IPN). This study compares the incidence and pattern of OXA-IPN between patients receiving FOLFOX-4 and XELOX. **Aim and objective:** To evaluate and compare the incidence and pattern of oxaliplatin-induced peripheral neuropathy in patients with colorectal cancer receiving FOLFOX-4 and XELOX. **Methods:** Sixty patients were selected via purposive sampling; 30 received FOLFOX-4 biweekly, and 30 received XELOX triweekly. OXA-IPN symptoms were assessed using the National Cancer Institute Neurosensory grading, NCI-CTCv5, Total Neuropathy Score (TNSc), and electrophysiological tests. Statistical analysis employed Chi-square and 'T' tests with significance set at $p < 0.05$. **Method:** Sixty patients were selected via purposive sampling; 30 received FOLFOX-4 biweekly, and 30 received XELOX triweekly. OXA-IPN symptoms were assessed using the National Cancer Institute Neurosensory grading, NCI-CTCv5, Total Neuropathy Score (TNSc), and electrophysiological tests. Statistical analysis employed Chi-square and 'T' tests with significance set at $p < 0.05$. **Result:** The incidence of acute OXA-IPN in group A receiving FOLFOX-4 is 86.7% & in group B receiving XELOX is 80.0%. Incidence of chronic OXA-IPN in group A & B is 80.0% & 56.7%, respectively. There was no significant difference in the incidence and severity of acute OXA-IPN, but the incidence of chronic OXA-IPN in patients receiving FOLFOX-4 was significantly higher (p-value -0.009). When the severity of chronic OXA-IPN is graded via NCI-CTC v5 and according to TNSc, the p-value is determined as 0.001 & 0.001, respectively, which is significant. Between-group comparisons of SAP changes of all three sensory nerves tested on two different follow-ups revealed significant differences. However, CMAP & MCV recorded on the peroneal nerve were insignificant. **Conclusion:** The incidence and severity of chronic oxaliplatin-induced peripheral neuropathy were significantly higher (p-value-0.009) in patients treated with FOLFOX-4 than with XELOX.

KEYWORDS: Oxaliplatin, peripheral neuropathy, FOLFOX-4, XELOX, colorectal cancer.

INTRODUCTION

Colorectal cancer (CRC) is a formidable global health challenge, ranking as the third most diagnosed cancer and the second leading cause of cancer-related mortality worldwide, according to the latest global cancer statistics.[1] In 2020 alone, CRC accounted for approximately 1.93 million new cases and led to 935,000 deaths globally, underscoring its significant public health impact and the urgent need for effective management strategies. Recent epidemiological trends reveal a complex picture: while incidence rates of CRC have been declining among older populations, there has been a concerning rise among younger age groups, with annual increases noted particularly in individuals aged 50 to 64 years and younger than 50 years.

In Bangladesh, CRC remains a major health burden, with statistics from Globocan 2020 reporting 2,753 new cases of colon cancer and 2,730 new cases of rectal cancer. These cancers accounted for significant mortality, claiming 1,772 lives due to colon cancer and 1,467 due to rectal cancer in the same year.[2] At the National Institute of Cancer Research and Hospital (NICRH) in Bangladesh, CRC cases constitute a notable proportion of gastrointestinal cancers treated, emphasizing their clinical significance and critical need for effective treatment modalities.

Oxaliplatin, a platinum-based chemotherapeutic agent, has become a cornerstone in the treatment of CRC, particularly in combination regimens like FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and XELOX.[3] These protocols are widely adopted in both adjuvant and metastatic settings due to their demonstrated efficacy in improving survival outcomes and disease-free intervals. Notably, FOLFOX-4 has emerged as a standard regimen in Western clinical practice, endorsed by clinical guidelines for its effectiveness in adjuvant therapy for Stage III CRC. Despite its therapeutic benefits, oxaliplatin is notorious for inducing significant peripheral neuropathy, known as oxaliplatin-induced peripheral neuropathy (OXA-IPN), which manifests in acute and chronic forms.[4] Acute OXA-IPN is characterized by transient sensory disturbances, often exacerbated by exposure to cold temperatures, and typically resolves shortly after treatment cessation. In contrast, chronic OXA-IPN develops cumulatively with prolonged exposure to oxaliplatin, leading to persistent sensory neuropathy that can significantly impair patient quality of life and treatment adherence.

The pathophysiology of OXA-IPN involves complex mechanisms, including the rapid chelation of calcium ions by oxalate released from oxaliplatin, leading to alterations in neuronal membrane potentials and subsequent neurotoxic effects. Chronic neuropathy results from the accumulation of platinum compounds within dorsal root ganglion cells, coupled with oxidative stress mechanisms that contribute to neuronal damage and dysfunction.[5] Risk factors for developing OXA-IPN include treatment regimen, cumulative dose of oxaliplatin, infusion duration, and pre-existing neuropathic conditions, highlighting the importance of tailored treatment approaches to mitigate neurotoxicity. Despite ongoing research efforts, effective prevention and management strategies for OXA-IPN remain elusive, underscoring the need for comparative studies to identify safer and more tolerable treatment regimens. The FOLFOX-4 and XELOX protocols represent two commonly used oxaliplatin-based regimens in CRC treatment, each with distinct dosing schedules and administration methods.[6] Understanding the differential impact of these regimens on the incidence and severity of OXA-IPN is crucial for optimizing treatment decisions and improving patient outcomes.

This study aims to contribute to this knowledge gap by evaluating and comparing the incidence and pattern of acute and chronic OXA-IPN in CRC patients treated with FOLFOX-4 versus XELOX regimens. By employing comprehensive clinical assessments, including the National Cancer Institute Neurosensory grading system, NCI-CTCv5 criteria, Total Neuropathy Score (TNSc), and electrophysiological testing, this study seeks to elucidate differences in neurotoxic profiles between the two treatment modalities.[7] Statistical analysis using chi-square tests and 'T' tests will be utilized to assess the significance of observed differences, with a predefined significance level of $p < 0.05$. Ultimately, findings from this study are anticipated to inform clinical practice guidelines and aid oncologists in selecting the optimal chemotherapy regimen that balances therapeutic efficacy with the minimization of treatment-related toxicity, thereby improving patient quality of life and treatment outcomes in CRC

OBJECTIVES

General objective

- To evaluate & compare oxaliplatin induced peripheral neuropathy among colorectal cancer patients receiving FOLFOX-4 and XELOX.

Specific objectives

- To find out the patients suffering from peripheral neuropathy by clinical assessment.
- To confirm and assess the peripheral neuropathy by the electrophysiological studies of the nerves to be affected.
- To evaluate the severity and grading of peripheral neuropathy by clinical assessment (National Cancer Institute Neurosensory grading of Oxaliplatin induced neurotoxicity, National Cancer Institute Common Toxicity Criteria, version & the clinical version of the Total Neuropathy Score) and electrophysiological studies in two modalities of treatment.

MATERIALS AND METHODS

Study Design

This study employed a quasi-experimental design to investigate the efficacy of FOLFOX-4 and XELOX regimens in patients with clinically diagnosed colon or rectal cancer at the National Institute of Cancer Research & Hospital, Dhaka. The study spanned from December 22, 2021, to November 21, 2022. The study population consisted of 60 patients, with 30 receiving FOLFOX-4 biweekly and another 30 receiving XELOX triweekly. Patients were selected based on clinical and histological confirmation of cancer. Data collection and analysis focused on treatment outcomes and patient response to chemotherapy.

Inclusion Criteria

- Patient with colon or rectal carcinoma receiving FOLFOX-4 or XELOX.

Exclusion criteria

- Previously diagnosed cases of peripheral neuropathy
- History of taking anti-TB drugs/anti-alcohol drugs (Disulfiram)/anticonvulsants (phenytoin)/amiodarone
- Co-morbidities like DM, renal or hepatic insufficiency.
- Pregnant or lactating Mother.
- Age <18 years or >70 years
- Patients with ECOG (Eastern Co-operative Oncology Group) performance status>2

Data collection

After 1st chemotherapy, a data collection sheet was used to detect the incidence of Acute Oxaliplatin induced Peripheral Neuropathy (OXI-PN), and National Cancer Institute Neurosensory grading of oxalplatin-induced neurotoxicity was used for recording the severity. Chronic cumulative OXA-IPN was graded using the National Cancer Institute common toxicity criteria, version 5.0 (NCI-CTCv5), where the clinical version of the Total Neuropathy Score (TNSc) was also used, and the incidence and severity were scored. Patients completed the data collection sheet at baseline first. Then, both data collection sheet & neurophysiological studies were carried out during cycle-6 (C6) and cycle-12 (C12) visits for FOLFOX-4 or cycle-4 (C4) and cycle-8 (C8) for XELOX.

An electrophysiological test was carried out for both upper and lower limbs on baseline & each follow-up visit. This study included motor and sensory amplitude and conduction velocities of upper and lower limb nerves. For the motor nerve conduction study, the amplitude and conduction velocity of the peroneal nerve of the lower limb were studied. The median and ulnar nerve at the wrist and sural nerve of the crossed limb were studied for the sensory conduction study. The last follow-up assessment was conducted within 1 month after the discontinuation of oxaliplatin based chemotherapy. No further follow-ups were formally planned afterward. All these data was recorded by a semi-structured questionnaire where the patient socio-demographic data was also noted. Then, the collected data was analyzed using the SPSS 25.0 version.

Data analysis

Statistical analyses were carried out by using the Statistical Program and Service Solution version 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as mean & standard deviation, and categorical variables are frequencies and percentages. The difference between groups was analyzed using the Chi-square test, t-test, and Fisher's exact test, shown with cross-tabulation. P-value <0.05 was considered as significant.

Ethical consideration

Ethical clearance from the Institutional Review Board (IRB) of the National Institute of Cancer Research and Hospital (NICRH) was approved on 11/04/2022 (Memo no.- NICRH/IRB/2022/112). After the conclusive recruitment of the subjects, the objective, nature, purpose, potential risks, and benefits of all the study procedures were explained in detail to the patients and informed written consent was obtained from them. Detailed history, clinical examination, performance status, and patient pretreatment condition were assessed. The record of this study was kept, and no names of the participants were used. The selected participants were given a Bangla version of consent to be read by them. If they voluntarily agreed to participate and give their full informed consent, they were only recruited as study subjects. Patients had the right to withdraw from this study any time. Privacy and confidentiality were maintained strictly.

RESULT

Table 1: Distribution of the study patients by baseline characteristics (n=60).

Variable	Group A (n=30)		Group B (n=30)		*p-value*
	N	%	N	%	
Age (in years)					
18-30	3	10.0	3	10.0	
31-39	7	23.3	6	20.0	
40-49	9	30.0	8	26.6	
50-59	7	23.3	9	30.0	
60-70	4	13.3	4	13.4	
Mean±SD	42.3±12.6		44.8±14.2		$^{a}0.328^{ns}$
Range (min-max)	18-68		18-69		
Sex					
Male	17	56.7	19	63.3	$^{b}0.485^{ns}$
Female	13	43.3	11	36.7	
Socio-economic condition (in Tk.)					
Poor (10,000)	22	73.3	20	66.7	
Lower middle class (10,001-30,000)	5	16.7	7	23.3	$^{b}0.287^{ns}$
Upper middle class (30,001-40,000)	2	6.7	3	10.0	
Upper class (>40,000)	1	3.3	0	0.0	

Educational Qualification					
Illiterate	7	23.3	9	30.0	
Primary	12	40.0	11	36.7	
SSC	6	20.0	7	23.3	$^{b}0.904^{ns}$
HSC	3	10.0	2	6.7	
Graduate or above	2	6.7	1	3.3	

ns=not significant [a]*p*-value reached from unpaired t-test [b]*p*-value reached from chi-square test

Table 1 revealed the distribution of the study patients by baseline characteristics; it was observed that the majority, i.e., 9(30.0%) patients, belonged to (the 40-49) years age group in group A and 9 (30.0%) belonged to (50-59) years age group in group B. In both groups, the majority was male. In group A, 17 (56.7%) patients, and in group B, 19(63.3%) patients were male. In group A, the majority, i.e., 22 (73.3%) patients, and in group B, 20(66.7%) patients came from poor socio-economic status. Most patients in both groups had primary pass, i.e., 12(40.0%) patients in group A and 11(36.7%) patients in group B.

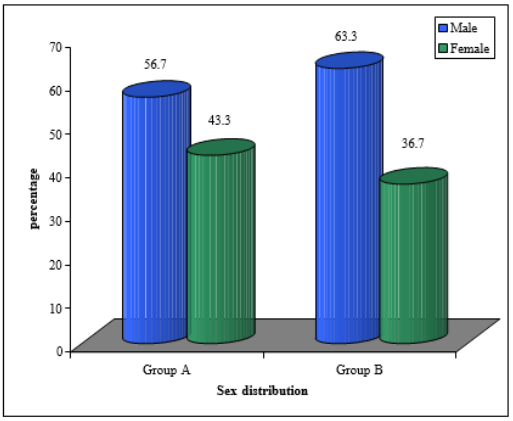

Figure 2: The bar diagram shows the sex group of the study.

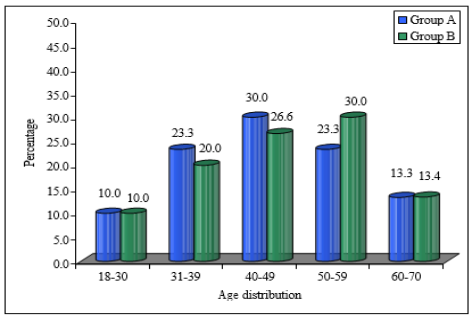

Figure 1: Bar diagram shows age group of the study patients.

Table 2: Differences in the incidence and severity of acute and chronic oxaliplatin-induced peripheral neuropathy in patients treated with FOLFOX-4 versus XELOX (n=60).

Variable	Group A (n=30)		Group B (n=30)		*p-value*
	N	%	N	%	
Incidence of acute OXA-IPN	26	86.7	24	80.0	0.556^{ns}
Severity of acute OXA-IPN					
Grade I	8	26.7	7	23.3	
Grade II	12	40.0	10	33.4	0.275^{ns}
Grade III	6	20.0	7	23.3	
None	4	13.3	6	20.0	
Incidence of chronic OXA-IPN	26	80.0	17	56.7	0.009^{s}
Severity of chronic OXA-IPN, according to NCI-CTCv5					
Grade I	4	13.3	10	33.3	
Grade II	15	50.0	5	16.7	0.001^{s}
Grade III	7	23.4	2	6.7	
None	4	13.3	13	43.3	
Severity of chronic OXA-IPN, according to TNSc					
Grade I	8	26.7	8	26.7	
Grade II	15	50.0	7	23.3	0.001^{s}
Grade III	3	10.0	2	6.7	
None	4	13.3	13	43.3	

Table 2 revealed that most (80.0%) of the colorectal cancer patients were suffering from chronic OXA-IPN (Oxaliplatin induced Peripheral Neuropathy) in group A, which was statistically significant (p value -0.009).

According to NCI-CTCv5 and TNSc grading system, the severity of chronic OXA-IPN in colorectal carcinoma patients is also statistically significant in group A (p value-0.001).

Table 3: Association between Peroneal CMAP (Compound Muscle Action Potential) with different follow-up (n=60).

Peroneal CMAP (mV)	Group A (n=30)	Group B (n=30)	*p-value*
	Mean±SD	Mean±SD	
Baseline	5.8±2.7	4.7±2.1	0.083^{ns}
Immediate follow-up	5.2±2.4	4.4±2.1	0.146^{ns}
Last, follow up	5.6±2.8	4.9±2.3	0.231^{ns}

Table 3 documented the association between Peroneal CMAP with different follow-ups. In baseline, the mean Peroneal CMAP was 5.8±2.7 (mV) in group A and 4.7±2.1 (mV) in group B. In the immediate follow-up, the mean Peroneal CMAP was 5.2±2.4 (mV) in group A and 4.4 ±2.1 (mV) in group B. In the last follow-up, the mean Peroneal CMAP was 5.6±2.8 (mV) in group A and 4.9±2.3 (mV) in group B. Immediate and last follow-ups were not statistically significant (p>0.05) between the two groups.

Table 4: Association between Peroneal MCV (Motor Conduction Velocity) with different follow-up (n=60).

Peroneal MCV (m/s)	Group A (n=30)	Group B (n=30)	*p-value*
	Mean±SD	Mean±SD	
Baseline	45.3±4.1	46.6±3.5	0.191^{ns}
Immediate follow-up	44.9±3.9	45.8±2.1	0.148^{ns}
Last, follow up	45.8±3.4	44.7±3.5	0.76^{ns}

Table 4 revealed an association between Peroneal MCV and different follow-ups; it was observed that in baseline, mean Peroneal MCV was 45.3±4.1 (m/s) in group A and 46.6±3.5 (m/s) in group B. In the immediate follow-up, the mean Peroneal a-MCV was 44.9±3.9 (m/s) in group A and 45.8±2.1 (m/s) in group B. In the last follow-up, the mean Peroneal MCV was 45.8±3.4 (m/s) in group A and 44.7±3.5 (m/s) in group B. Immediate and last follow-ups were not statistically significant (p>0.05) between the two groups.

DISCUSSION

Oxaliplatin is the key platinum anti-cancer agent used in treating colorectal cancer, either in combination with 5 FU (FOLFOX-4) or capecitabine (XELOX). Peripheral neuropathy is the most common debilitating side effect of oxaliplatin. This Quasi-experimental study was carried out to evaluate & compare the peripheral neuropathy induced by oxaliplatin among colorectal cancer patients receiving FOLFOX-4 with those receiving XELOX. A total of 60 patients with clinically diagnosed and histologically proven colon or rectal carcinoma was included in this study. Thirty samples were included in group A and treated with FOLFOX-4 two weekly for 12 cycles. Another thirty samples belonged to group B, who were treated with XELOX three weekly for a total of 8 cycles. These patients were admitted or attended the Department of Medical Oncology at the National Institute of Cancer Research and Hospital (NICRH), Dhaka. This study was conducted from December 22, 2021, to November 21, 2022. Both sexes were included. Patients who had not received the first line chemotherapy and had normal renal & liver function with ECOG performance status of 0 to 2 were included. Patients with a history of peripheral neuropathy, anti-TB drugs/anti-alcohol drugs (Disulfiram)/anticonvulsants (phenytoin)/amiodarone & other co-morbidities like DM, renal insufficiency, alcohol abuse (> 4IU/ day), pregnant or lactating mother & patients not willing to participate in this study were excluded from the study.

The age range for this study is 18 to 70 years. This study shows that almost one-third, i.e., 9(30%) patients, belonged to (40-49) years in group A, and 9 (30.0%) belonged to 50-59 years in group B. The mean age was 42.3 years in group A & 44.8 years in group B. Among all patients, the male & female ratio was 1.5. The majority was male in both arms. In group A, the number of male and female patients were 17 (56.7%) and 13 (43.3%), respectively, and the ratio was 1.3:1. In group B, male and female patients were 19 (63.3%) and 11 (36.7%), respectively. The ratio was 1.7:1. There was no significant difference (p>0.05) in mean age and sex between group A & group B. Davis *et al.* analyzed the rates of change in CRC incidence. It concluded that colorectal cancer in the young had continued to increase. The incidence remained low in the population less than 20 years of age. However, the increasing trend over the age of 20 became clear, with the most dramatic increase in the 40-to-44-year age group (approximately 67%). In a similar study, a population-based cross-sectional study that included 3349 subjects, Risk factor prevalences and adjusted Prevalence ratios (PRs) were higher for male gender and smoking than for family history of CRC. Population-attributable factors (PAFs) for the prevalence of non-advanced and advanced CRC were highest for the male gender (23% and 23%, respectively). The current study's findings correlated with them.[8]

Andre *et al.* found median age was 60 years in the FL plus Oxaliplatin group and 60 years in the FL group. The majority (56.1%) was male in the FL plus Oxaliplatin

group and 588(52.4%) in the FL group. A similar study shows 63.6% were males and 36.4% were females. In addition, 44.6% of the patients were 31–50 years old. A similar study found that the median age was 61 years in the Irinotecan and Fluorouracil Plus Leucovorin and 61 years in the Oxaliplatin and Fluorouracil Plus Leucovorin group. Almost two-thirds (65.0%) was male in the Irinotecan and Fluorouracil Plus Leucovorin and 157(59.0%) in the Oxaliplatin and Fluorouracil Plus Leucovorin group. A similar study observed that the median age was 66 years in the Arm A IRI/LV/5-FU group and 65 years in the Arm B OXA/LV/5-FU group.[9] Almost two-thirds (61.0%) were male in the Arm A IRI/LV/5-FU group and 92(62.0%) in the Arm B OXA/LV/5-FU group. Demographics and baseline characteristics were balanced between the two groups.[10] study shows that the mean age was 63.3±9.1 years in the FOLFOX-4 group and 63.7±8.8 years in the XELOX group. More than half (55.8%) were male in the FOLFOX-4 group and 47(64.3%) in the XELOX group. Two third (66.3%) were Adjuvant in the FOLFOX-4 group and 47(64.3%0 in the XELOX group. In group A, almost three-fourths, i.e., 22(73.3%), and in group B, 20 (66.7%) patients came from poor socio-economic status. A majority, i.e., 12(40.0%) patients in group A and 11(36.7%) in group B primary pass. In occupational status, half, i.e., 15(50.0%) patients in group A and 17(56.7%) patients in group B were farmers.[11]

Slattery *et al.*. is a population-based case-control study of colon cancer conducted in 3 areas in the United States. It was observed that approximately a 50% increase occurred in colon cancer risk from smoking over a pack of cigarettes per day among both men and women. Those who stopped smoking remained at increased risk, even if they stopped over 10 years ago. Support the association of smoking with colon & rectal cancer. In this present study, it was observed that 25 patients (83.3%) in group A and 13 patients (43.33%) in group B had colon cancer. Rest had rectal cancer, i.e., 5 (16.6%) & 17 (56.67%) patients in groups A & B, respectively. The difference was statistically insignificant ($p>0.05$) between the two groups. In the study, almost two-thirds (63.0%) of patients had colon site tumour in the FOLFOX4 group and 66.0% in the FOLFOX4- placebo group. Another study also found almost a fourth (72.0%) had colon sites in the Arm A IRI/LV/5-FU group and (70.0%) in the Arm B OXA/LV/5-FU group.[12]

In this study, the incidence of acute OXA-IPN is 26(86.7%) in group A and 24(80.0%) in group B. Regarding severity, the majority had grade II acute OXA-IPN in both groups, i.e., 12 (40.0%) patients in group A and 10(33.4%) in group B. P-value was insignificant when comparing the incidence & severity of acute OXA-IPN between these two groups. Incidence of chronic OXA-IPN is 26(80.0%) in group A and 17(56.7%) in group B, which is significant (P-value-0.009). In severity of chronic OXA-IPN, according to NCI-CTCv5, in group A, half of the patients- 15 (50%) experienced Grade II peripheral neuropathy, then 7 (23.4%) experienced grade III & 4 (13.3%) experienced grade I. No chronic OXA-IPN was recorded in 4 (13.3%). In group B, 10(33.3%) experienced grade I peripheral neuropathy, then 5 (16.7%) had grade II & 2 (6.7%) had grade III peripheral neuropathy. Here, 13(43.3%) did not develop chronic OXA-IPN in group B. In the severity of chronic OXA-IPN, according to TNSc, in group A, 15(50.0%) patients had grade II peripheral neuropathy, 8 (26.7%) had grade I & 3(10%) experienced grade III peripheral neuropathy. In group B, 8(26.7%) patients had grade I, then 7(23.3%) patients had grade III & 2(6.7%) had grade II peripheral neuropathy. In groups A & B, 4 (13.3%) & 13 (43.3%) patients did not develop chronic OXA-IPN. The severity of chronic OXA-IPN, according to NCI-CTCv5, and the severity of chronic OXA-IPN, according to TNSc, were statistically significant ($p<0.05$) between the two groups.

Argyriou *et al*., observed a comparison of OXA-IPN incidence between groups. No statistically significant difference was observed in the incidence of acute OXA-IPN, which was present in 65/77 of FOLFOX-4-treated patients (84.4%) and in 60/73 of patients treated with XELOX (79.5%; P = 0.525). In contrast, FOLFOX- 4 was associated with an increased incidence of cumulative neurotoxicity compared with XELOX-treated patients (n = 64/ 77 versus 44/73; chi-square P = 0.002). The OXA cumulative dose was significantly associated with the development of chronic OXA-PN in both the groups (r = 0.254; P = 0.026 for FOLFOX-4 and 0.252; P = 0.031 for XELOX), but it has not influenced the manifestation of acute neurotoxicity during treatment with either regimen. According to the evaluation of acute neurotoxicity intensity at the final follow-up, the median number of symptoms that patients reported was 3 (range 1–7) both in the FOLFOX-4 and in the XELOX group (P = 0.280), and the sum number of acute symptoms was also similar. According to NCICTCv3, 19/77 patients treated with FOLFOX-4 experienced grade 1 chronic OXA-IPN (24.7%), 37/77 experienced grade 2 (48.1%), while grade 3 was revealed in eight cases (10.4%). Comparatively, XELOX-treated patients had lower overall rates of OXA-IPN severities than the FOLFOX-4-treated patients (P < 0.001). The same observation emerged using the TNSc scale, with a higher severity of cumulative OXA-IPN in patients treated with FOLFOX-4 than with XELOX. Accordingly, the TNSc mean values were statistically different between groups (7.3 ± 4.4 for FOLFOX versus 5.7 ± 5.4 for XELOX; P = 0.046). Similar results were obtained when only the sensory components of the TNSc (sum score of TNSc item 1 + 4 + 5) were considered (3.9 ± 2.7 for FOLFOX versus 3.0 ± 3.0 for XELOX; P = 0.048).[13]

Baek *et al.,* was a prospective study in which OXCPN was recorded for all consecutive colon cancer patients treated at Samsung Medical Center (Seoul, Korea) with oxaliplatin-based combination chemotherapy. The primary endpoint was the incidence of severe OXCPN

(grade 2 lasting for >7 days, or grade 3). A multivariate regression model evaluated the association of severe OXCPN and pretreatment parameters. Between Jan 2008 and Feb 2010, 100 patients were registered with adjuvant FOLFOX, and 266 patients were treated with XELOX for advanced disease.[14]

Results showed severe OXCPN was frequently observed in patients with age ≥55 years (p<0.01), stage II or III (p<0.01), adjuvant setting (p=0.01), FOLFOX (p<0.01), performance status of 0 (p=0.02), and those with no prior chemotherapy (p<0.01). In this present study, it was observed that the mean Ulnar a-SAP was 14.8±6.8 (μV) in group A and 12.8±7.2 (μV) in group B. In the immediate follow-up, mean Ulnar a-SAP was 12.6±6.9 (μV) in group A and 9.4±3.9 (μV) in group B. In the last follow-up, mean Ulnar a- SAP was 7.1±4.1 (μV) in group A and 4.9±3.8 (μV) in group B. Immediate and last follow-up showed a statistically significant difference between the two groups in a-SAP (p<0.05). A similar study observed that mean Ulnar a-SAP was 15.3±7.6 (μV) in the FOLFOX-4 group and 13.0±7.4 (μV) in the XELOX group.[15] In the immediate follow-up, mean Ulnar a-SAP was 13.4±7.1 (μV) in the FOLFOX-4 group and 9.9±4.8 (μV) in the XELOX group. In the last follow-up, mean Ulnar a-SAP was 6.4±4.9 (μV) in the FOLFOX-4 group and 5.6±4.3 (μV) in the XELOX group. In this present study, the mean Median a-SAP was 18.6±7.6 (μV) in group A and 15.1±7.4 (μV) in group B. In the immediate follow-up, the mean Median a-SAP was 14.8±8.9 (μV) in group A and 9.9±4.6 (μV) in group B. In the last follow-up, the mean Median a-SAP was 7.6±5.6 (μV) in group A and 4.9±4.1 (μV) in group B. Immediate and last follow-up showed a statistically significant difference between the two groups in a-SAP (p<0.05). A similar study observed that mean Radial a-SAP was 19.1±9.4 (μV) in the FOLFOX-4 group and 13.6±7.8 (μV) in the XELOX group. In the immediate follow-up, mean Radial a-SAP was 15.9±9.1 (μV) in group A and 10.7±5.1 (μV) in the XELOX group. In the last follow-up, mean Radial a-SAP was 8.2±6.1 (μV) in the FOLFOX-4 group and 6.2±5.3 (μV) in the XELOX group.[16]

This present study shows that the mean Sural a-SAP was 13.4±4.7 (μV) in group A and 12.9±3.9 (μV) in group B. In the immediate follow-up, mean Sural a-SAP was 9.6±4.8 (μV) in group A and 12.1±3.6 (μV) in group B. In the last follow-up, mean Sural a-SAP was 5.8±4.4 (μV) in group A and 8.6±5.6 (μV) in group B. Immediate and last follow-up were statistically significant (p<0.05) between the two groups. A similar study observed that mean Sural a-SAP was 13.0±5.1 (μV) in the FOLFOX-4 group and 13.7±4.6 (μV) in the XELOX group. In the immediate follow-up, mean Sural a-SAP was 10.1±3.9 (μV) in the FOLFOX-4 group and 10.4±4.3 (μV) in the XELOX group. In the last follow-up, mean FOLFOX-4 was 6.1±5.1 (μV) in the FOLFOX-4 group and 6.9±6.2 (μV) in the XELOX group.[17] In this present study, the mean CMAP recorded on a peroneal nerve in group A was 5.8±2.7(mV), 5.2±2.4(mV) & 5.6±2.8(mV), respectively on baseline, immediate follow-up and last follow up. Mean CMAP in Group B was 4.7±2.1(mV), 4.4±2.1(mV) & 4.9±2.3(mV), respectively, on the baseline, immediate follow-up, and last follow-up. The immediate and last follow-ups were not statistically significant (p>0.05) between the two groups.

Mean peroneal MCV was 45.3±4.1 (m/s) in group A and 46.6±3.5 (m/s) in group B on baseline. In immediate follow-up, mean Peroneal MCV was 44.9±3.9 (m/s) in group A and 45.8±2.1 (m/s) in group B. In the last follow-up, the mean peroneal MCV was 45.8±3.4 (m/s) in group A and 44.7±3.5 (m/s) in group B. Immediate and last follow-ups were statistically non-significant (p>0.05) between the two groups. A similar study observed that mean Peroneal a-CMAP was 6.4±3.1 (mV) in the FOLFOX-4 group and 5.0±2.3 (mV) in the XELOX group. In the immediate follow-up, the mean Peroneal a-CMAP was 6.1±3.0 (mV) in the FOLFOX-4 group and 4.8±2.4 (mV) in the XELOX group. In the last follow-up, the mean Peroneal a-CMAP was 6.3±2.9 (mV) in the FOLFOX-4 group and 4.8±2.3 (mV) in the XELOX group.[18] Argyriou *et al.*'s study also observed that mean Per/al a-MCV was 47.7±4.7 (m/s) in the FOLFOX-4 group and 48.1±3.6 (m/s) in the the XELOX group. In immediate follow-up, mean Per/al a-MCV was 46.3±3.5 (m/s) in the FOLFOX-4 group and 46.8±2.5 (m/s) in the XELOX group. In the last follow-up, the mean Peroneal a-MCV was 46.8±3.7 (m/s) in the FOLFOX-4 group and 47.9±3.3 (m/s) in the XELOX group. In this study, both a-MCV & CMAP changes on subsequent follow-ups were also non-significant.[19]

CONCLUSION

After analyzing the results of this study, it can be concluded that the incidence and severity of chronic oxaliplatin induced peripheral neuropathy in colorectal cancer patients receiving FOLFOX-4 is significantly higher than those receiving XELOX. There is also a significant difference in neurophysiological changes recorded on sensory nerves. However, the incidence and severity of acute oxaliplatin induced peripheral neuropathy does not significantly differ in these two groups.

Recommendation

The result of this study shows that the incidence & severity of cumulative/chronic neuropathy are significantly greater with the FOLFOX-4 protocol than with XELOX, along with neurophysiological changes on sensory nerves. The efficacy of FOLFOX-4 & XELOX as 1st line therapy remains inferior to each other in different trials. They are category 1 treatments for colorectal cancer both in non-metastatic & metastatic settings according to different guidelines, including NCCN. XELOX can be considered for the treatment of colorectal cancer instead of FOLFOX-4 when indicated to reduce morbidity and to increase the quality of life,

especially in young patients who have more expected survival than older population.

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