Effect of diabetes on neurological adverse effects and chemotherapy induced peripheral neuropathy in advanced colorectal cancer patients treated with different FOLFOX regimens

Nusrat Bano[1] and Rahila Ikram[2]
[1]Department Pharmacology, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[2]Department Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

Abstract: This retrospective study reports impact of diabetes on incidence rate of dose limiting symptoms of neurological toxicity and chemotherapy induced peripheral neuropathy (CIPN). Post-surgical colorectal cancer (CRC) patients with metastatic disease, treated with four different schedules of FOLFOX were included in this study. Neurological adverse effects were assessed by CTC v2.0. The incidence rate of adverse neurological symptoms in CRC patients, clinically diagnosed with diabetes (n=6) were compared with non-diabetic CRC patients (n=32). The results show that the difference in the incidence rate of paresthesia is significant (p=0.043) between diabetic and non-diabetic patients. The difference in the incidence rates of hypoesthesia (p=0.445), peripheral neuropathy (p=0.889), dizziness (p=0.445), insomnia (p=0.690), taste disturbances (p=0.258), and headache (p=0.498) in diabetic and non-diabetic CRC patients was not significant. The findings indicate that risk of frequent, distal and transient paresthesia within the first few minutes of Oxaliplatin infusion is higher in diabetic CRC patients.

Keywords: Diabetes, FOLFOX, colorectal, peripheral neuropathy.

INTRODUCTION

Chemotherapy induced peripheral neuropathy (CIPN) is a dose limiting and debilitating adverse effect in cancer patients (Schloss *et al*., 2017). Patient related outcomes are usually worse in cancer patients which also suffer from diabetes (Vissers *et al*. 2016). Diabetic patients are at higher risk to develop chemotherapy induced peripheral neuropathy (Hershman *et al*. 2016). Incidence rate, onset time and intensity of neurological symptoms of CIPN are varied in diabetic and non-diabetic patients (Leon-Ferre *et al*. 2017). CIPN is associated with axonal degeneration, damaged microtubule-mediated axonal transport, mitochondrial dysfunction and direct dorsal root ganglion damages (Addington and Freimer, 2016). Diabetic patients are prone to neuronal toxicity associated with axonal loss due to reduced axonal regeneration (Khoshnoodi *et al*., 2017). Although, aetiology specific dissimilarities exist for chronic distal symmetrical peripheral sensory neuropathy associated with either diabetes or cancer chemotherapy (Zheng *et al*., 2012) however, drugs like duloxetine and metformin indicated primarily for diabetes and diabetic neuropathy are shown to bear therapeutic efficacy against CIPN (Shapiro 2016; Mao-Ying *et al*., 2014).

Oxaliplatin induced peripheral neuropathy can be acute or chronic. Acute CIPN is a neurosensory neurotoxicity characterized by jaw tightness, dysesthesias and paresthesia of feet, hands and perioral region which is rapidly reversible and occurs shortly after infusion (Carozzi *et al*., 2015). Chronic sensory neuropathy, on the other hand usually develops after a cumulative dose of 540 mg/m^2 over four or more cycles. It is associated with sensory ataxia, distal paresthesia, functional impairment, jaw and eye pain, leg cramps, ptosis and voice and visual disturbances (Carozzi *et al*., 2015). There are few studies that report direct association of diabetes with higher incidence rate or severity of CIPN in cancer patients treated with Oxaliplatin (Uwah *et al*., 2012; Wolf *et al*. 2008).

In this research study, we hypothesized that history of diabetic disease induces and intensifies CIPN and some associated neurological adverse symptoms (paresthesia**,** taste disturbances, hypoesthesia, headache, insomnia and dizziness) in advanced CRC patients treated with oxaliplatin based chemotherapy.

MATERIALS AND METHODS

This retrospective observational study was conducted in KIRAN (Karachi Institute of Radiotherapy and Nuclear Medicine), Pakistan, following institutional authorization and ethical approval. Forty seven patients scheduled for treatment with FOLFOX regimen were included in this study. Patient profile was maintained with an assigned number to maintain privacy. By the end of the study, only thirty eight patients (38) were evaluable and assessable. Thirty two patients had normal glucose levels with no prior history of diabetes whereas six patients had previous clinical diagnosis and history of diabetes with impaired fasting glucose levels assessed throughout the course of therapy. All diabetic patients were maintained on required

**Corresponding author:* e-mail: nusratbano@hotmail.com

doses of insulin during the course of treatment. An inclusion criterion was based on following considerations:

1. Histologically confirmed metastatic colorectal cancer
2. Acceptable CBC and Serum creatinine clearance lab reports prior to chemotherapy
3. Age ranging from 20-80 years
4. Eastern cooperative oncology group (ECOG) performance status ≤3 prior to chemotherapy
5. Absence of active ulcer (since 12 months)
6. No diagnosed renal, hepatic and cardiac impartment prior to chemotherapy
7. No preexisting neuropathy

Data of seven patients was excluded due to cessation of therapy or discontinuation/alteration of FOLFOX regimen. Two patients with history of diabetes and treated with mFOLFOX were initially included in the study but their treatment regimens were shifted after three cycles of mFOLFOX in line with CT-scan results. Therefore, clinical data of those two patients was not included in our study. An incidence report form was generated to identify the listed neurological adverse effects (e.g. taste disturbances, hypoesthesia, headache, insomnia, dizziness, paresthesia and peripheral neuropathy) after each cycle of treatment in every patient and denote the severity of the symptom. A single adverse event was treated as one incident report. Neurological adverse effects were graded on a scale of 1-5 as per grade definition of Common toxicity criteria CTC v 2.0. For assessment of dysesthesia and paresthesia, Oxaliplatin Specific Neurotoxicity Scale (OSNS) (Cassidy and Misset, 2002) was utilized: Grade 1-paresthesia or dysesthesia that regressed completely before the next treatment cycle; Grade 2-paresthesia or dysesthesia that persisted between therapeutic courses; and Grade 3-paresthesia or dysesthesia causing impairment in functions (Cassidy and Misset, 2002). Clinical signs and symptoms clearly associated with features of CRC were excluded. The adverse effects were clinically assessed after every dose administration for each chemotherapeutic round in all of the treatment arms.

Chemotherapy was administered following initial assessment of baseline biochemical profile including CBC and CEA. Fig. 1 shows the oxaliplatin based investigational chemotherapeutic protocols. Cycles were repeated after two weeks (every 14 days). Doses started with central line placement and IV initiated with distilled water. Premedication with 5HT3RA and Dexamethasone 20 mg in 100 cc D5W was given along with mild to moderate emetogonic protocol during treatments. Supportive therapy comprising of filgrastim, pegfilgrastim, darberpoetin alpha or epoetin alpha (for bone marrow depression Nadir 10-14 days) was initiated if required in any particular case indication. Antidiarrheal protocol comprised of treatment with loperamide and diphenoxylate /atropine sulphate as required.

Frequency of neurological adverse effect reports in diabetic patients was compared with the non-diabetic patients by independent sample *t test*. The incidence rate of neurological adverse effects was also compared between diabetic and non-diabetic patients in each treatment arm. SPSS version 19 was used for analysis of data. *p* value less than 0.001 was considered very highly significant, *p* value less than 0.01 was considered highly significant whereas *p* value less than 0.05 was considered significant.

Ethical approval

For this type of study based on retrospective design, formal consent is not required. Institutional authorization was signed. The study protocol was designed and conducted in line with WMA Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013).

RESULTS

Fig. 2 shows the incidence rate of each adverse effect and severity of the symptoms with related frequency. In FOLFOX 4 treatment arm, the maximum number of cycles included for any patient was 12 cycles whereas 10 was the median number of cycles. There were 60 incidence reports of grade 1 paresthesia. Mild Paresthesia was the most frequently reported neurological adverse effect in FOLFOX4 treatment arm. Severity of symptom was noted for Peripheral neuropathy (19 incidence reports of Grade 2 and 12 incidence reports of Grade 3) in FOLFOX4 treatment arm (fig. 2a).

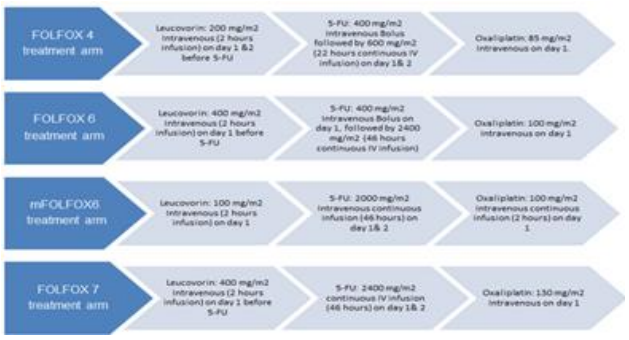

Fig. 1: Doses of oxaliplatin in different FOLFOX treatment arms.

In FOLFOX6 treatment arm (Fig. 2b), median number of cycle was 6 whereas 8 cycles of treatment was the maximum given to any patient. There were 39 incidence reports of mild taste disturbance (grade 1) and 28 incidence reports of Grade 1 Headache documented in FOLFOX 6 treatment arm. Insomnia was a symptom with the lowest incidence rate (7 incidence reports) in FOLFOX6 treatment arm. The only symptom reported

Table 1: Implications of previous diabetic disease on neurological toxicity in CRC patients treated with FOLFOX

Independent Sample t test							
		Gender	Mean	Std. Deviation	Mean Difference	T	p value
Neurological Adverse effects	Taste Disturbance	Diabetic	2.333	2.582	-1.792	-1.148	0.258
		Non	4.125	3.635			
	Paresthesia	Diabetic	4.000	3.286	2.313	2.099	0.043
		Non	1.688	2.320			
	Headache	Diabetic	4.167	3.488	-1.083	-0.685	0.498
		Non	5.250	3.565			
	Dizziness	Diabetic	3.000	2.449	1.813	1.788	0.082
		Non	1.188	2.250			
	Insomnia	Diabetic	1.833	2.563	0.427	0.403	0.690
		Non Diabetic	1.406	2.354			
	Peripheral Neuropathy	Diabetic	5.333	3.204	-0.229	-0.140	0.889
		Non	5.563	3.750			
	Hypoesthesia	Diabetic	3.333	3.559	-1.417	-0.771	0.445
		Non	4.750	4.212			

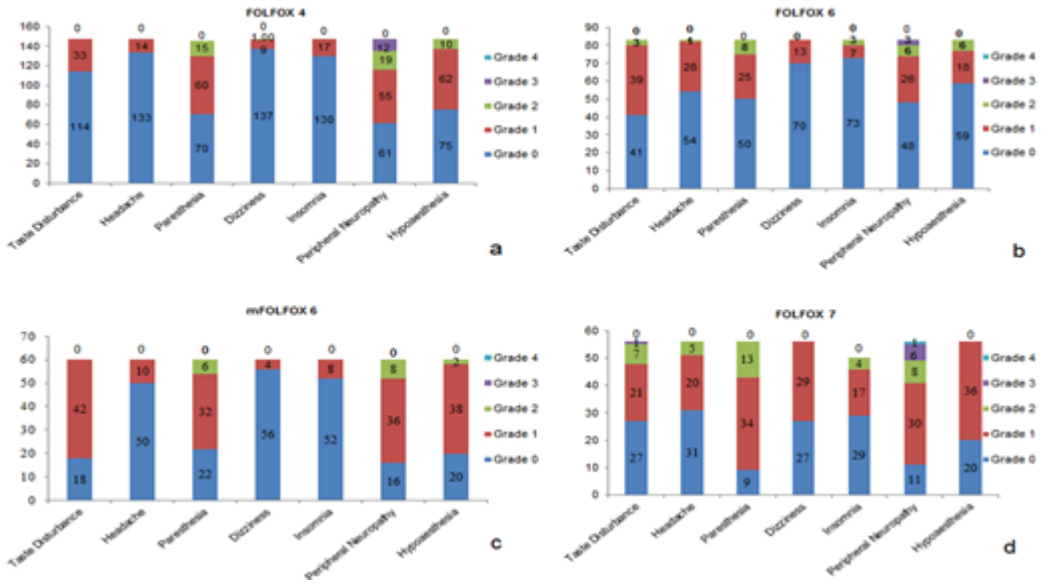

Fig. 2: Incidence rate of neurological adverse effects in advanced CRC patients treated with different FOLFOX regimens. Grade 1 (mild adverse effect); Grade 2 (moderate adverse effect); Grade 3 (severe and undesirable adverse effect); Grade 4 (life threatening or disabling adverse effect).

with Grade 3 on severity scale was Peripheral neuropathy (3 incidence reports). There were 8 incidence reports of Grade 2 Paresthesia FOLFOX6 treatment arm. Toxicity was observed in mFOLFOX 6 arm (median number of cycle was 12). The maximum treatment comprised of 12 cycles in any patient in this treatment group. There were 42 incidence reports of mild taste disturbances (Grade 1) in mFOLFOX6 patients (fig. 2c). There were no reports of grade 3 or 4 neurological toxicity in patients of mFOLFOX6 treatment arm. Severity of symptoms of peripheral neuropathy (grade 2) was noted in eight incidence reports. In the FOLFOX7 treatment arm median number of cycle was 8, whereas, patients received a maximum of 9 treatments in this group. There were 36 incidence reports of grade 1 Hypoesthesia in FOLFOX7 patients (fig. 2d). Severe peripheral neuropathy was reported in FOLFOX7 patients (6 incidence reports of grade 3 and 1 incidence report of grade 4).

Table 1 shows no significant difference in incidence rates of taste disturbance (p=0.258) between diabetic and non-diabetic patients. Paresthesia is reported more in diabetic patients and the difference in the incidence rate of diabetic and non-diabetic patient is significant (p= 0.043). Diabetic patients experienced more dizziness but the overall difference between the two group of patients is not

Table 2: Comparative effects of diabetic disease on neurological toxicity in different treatment arms of FOLFOX

Independent Sample t test								
		Type	Diabetic	Mean	Std. Deviation	Mean Difference	t	p value
Neurological	Taste Disturbance	FolFox4	Diabetic	0.000	0.000	-3.000	-1.050	0.316
			Non Diabetic	3.000	3.899			
		FolFox6	Diabetic	2.500	3.536	-1.200	-0.675	0.515
			Non Diabetic	3.700	2.111			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	8.400	4.615			
		FolFox7	Diabetic	4.500	0.707	1.167	0.749	0.482
			Non Diabetic	3.333	2.066			
	Paresthesia	FolFox4	Diabetic	4.000	5.657	3.455	2.135	0.056
			Non Diabetic	0.545	1.293			
		FolFox6	Diabetic	2.500	3.536	0.100	0.045	0.965
			Non Diabetic	2.400	2.757			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	2.000	2.000			
		FolFox7	Diabetic	5.500	0.707	3.167	1.435	0.201
			Non Diabetic	2.333	2.944			
	Headache	FolFox4	Diabetic	7.500	0.707	2.045	0.585	0.570
			Non Diabetic	5.455	4.762			
		FolFox6	Diabetic	0.000	0.000	-3.300	-1.767	0.108
			Non Diabetic	3.300	2.541			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	7.600	2.408			
		FolFox7	Diabetic	5.000	1.414	-1.167	-0.853	0.426
			Non Diabetic	6.167	1.722			
	Dizziness	FolFox4	Diabetic	3.500	4.950	3.227	2.600	0.025
			Non Diabetic	0.273	0.647			
		FolFox6	Diabetic	3.000	0.000	2.300	1.657	0.128
			Non Diabetic	0.700	1.889			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	0.800	1.304			
		FolFox7	Diabetic	2.500	2.121	-1.500	-0.588	0.578
			Non Diabetic	4.000	3.286			
	Insomnia	FolFox4	Diabetic	3.500	3.536	2.591	1.342	0.207
			Non Diabetic	0.909	2.386			
		FolFox6	Diabetic	0.000	0.000	-1.000	-0.630	0.543
			Non Diabetic	1.000	2.160			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	1.600	2.191			
		FolFox7	Diabetic	2.000	2.828	-0.833	-0.373	0.722
			Non Diabetic	2.833	2.714			
	Peripheral Neuropathy	FolFox4	Diabetic	8.500	0.707	2.227	0.696	0.501
			Non Diabetic	6.273	4.361			
		FolFox6	Diabetic	2.500	3.536	-0.500	-0.272	0.791
			Non Diabetic	3.000	2.211			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	8.800	2.950			
		FolFox7	Diabetic	5.000	1.414	-0.833	-0.373	0.722
			Non Diabetic	5.833	2.927			
	Hypoesthesia	FolFox4	Diabetic	4.500	6.364	-1.227	-0.316	0.758
			Non Diabetic	5.727	4.901			
		FolFox6	Diabetic	1.500	2.121	-0.600	-0.308	0.765
			Non Diabetic	2.100	2.558			
		mFolFox6	Diabetic	.	.			
			Non Diabetic	8.000	4.637			
		FolFox7	Diabetic	4.000	2.828	-0.667	-0.319	0.761
			Non Diabetic	4.667	2.503			

statistically significant (p=0.082). Table 2 shows that in the FOLFOX 4 treatment arm, incidence rate of dizziness is higher in diabetic patients and the difference between diabetic and non-diabetic patients is statistically significant (p=0.025).

DISCUSSION

The study shows that the frequency and onset of neurological adverse symptoms is not markedly different in diabetic CRC patients compared to non-diabetic CRC patients treated with FOLFOX. These results are different than findings reported by Vissers *et al*. (2015), showing that diabetic CRC patients have increased mild to moderate neuropathic symptoms burden. In our study, we do not see a significant difference in the incidence rate of chemotherapy induced neurological symptoms like taste disturbance, headache, insomnia, CIPN or hypoesthesia between the two group of patients. On the other hand, our findings are in line with studies which did not report an association between diabetes as a predictor in development of neuropathy (Brouwers *et al*., 2009; Dimopoulos *et al*., 2011; Vincenzi *et al*., 2013).

It was observed in our study that Paresthesia is more frequently reported in diabetic patients and the difference in the incidence rate between the two groups of patient is statistically significant (p=0.043). Patients with pre-existing neurological risk conditions like diabetes are previously shown to experience exacerbation of chemotherapy associated neurological adverse effects (Custodio, 2017). It is observed in advanced CRC diabetic patients treated with FOLFOX 4 in the present study as significant difference (p=0.056) between the frequency of paresthesia in diabetic and non-diabetic patient exists mostly in this treatment arm. Paresthesia is also associated with postural instability in diabetic patients (Morimoto *et al*., 2016) which may require risk assessment in diabetic CRC patients treated with FOLFOX. Onset of Grade 2 paresthesia necessitates that doses of oxaliplatin be reduced to one ($75mg/m^2$) or two ($50mg/m^2$) levels upon persistence of symptoms (Tournigand *et al* 2004). Therapeutic approaches to reduce oxaliplatin induced neurotoxicity require modulation of sodium channel inactivation properties (Park *et al*. 2011). The incidence rate of dizziness in diabetic patients of FOLFOX4 treatment arm is higher than the non-diabetic CRC patients in this treatment arm. The difference in the frequency of dizziness in diabetic and non-diabetic patient of FOLFOX4 treatment arm is significant (p=0.025). Dizziness is associated with flushing or blood pressure changes and fainting during treatment with antineoplastic agents (Morgan and Kauffmann, 2017). It is also associated with polyuria and hypoglycemia in diabetic patients (Fisher, 2017). Sensorial perception distortion was also observed in one of the diabetic patient (FOLFOX 4 treatment arm) experiencing dizziness shortly after chemotherapeutic infusion. This symptom can be attributed to oxaliplatin induced CIPN since neuropathy due to cancer chemotherapy can be associated with multiple sensorial perception distortions (Cavero and Holzgrefe, 2017). tables 1 and 2 also show that the risk of other neurological adverse effects e.g. tastes disturbances, hypoesthesia, headache, insomnia and peripheral neuropathy lies evenly for CRC patients with and without diabetes treated with FOLFOX regimen. Non-steroidal anti-inflammatory (NSAIDS) drugs are reported to bear considerable efficacy in oxaliplatin induced neuropathy (Kanbayashi *et al*., 2010). In our study NSAIDS were not found to be effective in any of the diabetic patients with CIPN but provided considerable relief in few non-diabetic patients experiencing acute neuropathy. The limitation of the study lies in limited number of diabetic patients which were not categorized upon severity of hyperglycemia. The use of oral antidiabetic medications e.g. metformin, which may affect CIPN occurrence, was not used as a statistical predictor in our observational study. Another factor that might also affect our results is that we did not assess self-reported neuropathy and documented only outcomes of clinical diagnoses tools. The response of interventions for therapeutic interventions for management of CIPN in diabetic and non-diabetic patients during the course of treatment can further be assessed.

CONCLUSION

Diabetic patients treated with different schedules of FOLFOX are not shown to have higher incidence rate of CIPN compared to non-diabetic patient. Dizziness is more frequently reported in diabetic cancer patients. The risk of frequent, distal and transient paresthesia shortly after Oxaliplatin infusion is higher in diabetic CRC patients.

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DISCLOSURE

The present study based on observational data included in this manuscript, is a part of a larger study, conducted in Karachi Institute of Radiotherapy and Nuclear Medicine (KIRAN), Pakistan after institutional authorization by Dr. Nusrat Bano (Principal investigator & first author) under the supervision of Prof. Dr. Rahila Ikram(research supervisor & second author).

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