RESEARCH ARTICLE

Gastrointestinal Adverse Effects in Advanced Colorectal Carcinoma Patients Treated with Different Schedules of FOLFOX

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Abstract

Background: To assess the frequency and severity of gastrointestinal adverse effects in advanced colorectal carcinoma patients treated with four different schedules of FOLFOX. Materials and Methods: Patients (median age 61 years) who underwent surgery were included in the study. All had measureable disease at CT scan, ultrasonography or clinical examination. Toxicity was graded on a scale of 1-5 according to the general grade definition of CTC v2.0. The severity of adverse effects (Grade 3 and 4) assessed in each treatment arm was compared. Results: Differences between the incidence rates of 3 and 4 toxicity and all grades of toxicity for all parameters in GI toxicity were very highly significant ($p<0.001$). Severe gastrointestinal symptoms of toxicity were noted with FOLFOX7 (oxaliplatin 130 mg/m^2). Grade 3 diarrhea was reported in 25% patients and grade 4 diarrhea in 4% in the FOLFOX7 treatment arm. Grade 2 vomiting was very frequently reported in the FOLFOX4 treatment arm (oxaliplatin 85mg/m^2). Grade 2 stomatitis was reported in 42% patients treated with mFOLFOX6 (oxaliplatin 100mg/m^2). Differences in the incidence rate of nausea, diarrhea and stomatitis among all treatment arms of FOLFOX were significant ($p<0.05$) . Conclusions: Severe diarrhea is associated with FOLFOX7 treatment. No grade 3 or 4 GI toxicity was reported in patients of the mFOLFOX6 arm.

Keywords: FOLFOX - colorectal carcinoma - stomatitis - diarrhea - nausea and vomiting

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Introduction

Incidence of toxicity for most diseases are reported on the presence or absence of relative adverse effects but in case of chemotherapy induced toxicity i.e. nausea, vomiting, stomatitis or diarrhea, it is limited to the report of severity of the symptoms (Carlotto et al., 2013). Oral and gastrointestinal mucositis/stomatitis are frequently reported in myelosuppressive chemotherapy of solid cancer (Schultheis et al., 2013). Colorectal cancer (CRC) is the third most frequent and top commonly diagnosed solid cancer in the world (Halit et al., 2012; Joanne et. al., 2013). The main therapeutic intervention for CRC is surgery (Dogan et al., 2011), whereas, most common and effective chemotherapeutic regimen in CRC is FOLFOX (Qi et al., 2013). Oxaliplatin in combination with 5FU/LV has effectively increased the progression free survival in patients of colorectal carcinoma (Bano et al., 2013a). The severity of gastrointestinal adverse effects associated with 5FU/LV chemotherapy is increased with the incorporation of oxaliplatin in the regimen (Bano and Najam, 2013b; Bano et al., 2013c) FOLFOX4 is associated with grade 3 or 4 diarrhea (Uncu et al., 2013) and nausea/vomiting (Lee et al., 2013) which is endured with effective supportive protocol. Diarrhea is a frequent dose limiting toxicity of FOLFOX (Comeau and Mohundro, 2013) *Lactobacillus spp* containing probiotic treatment is recommended in chemotherapy or radiotherapy induced diarrhea (Gibson et al., 2013). Nausea and vomiting can be effectively managed by dexamethasone and indisetron in optimal doses in approximately 80% cases (Nakatsumi et al., 2013). The present study reports the incidence rate and severity of chemotherapy induced gastrointestinal adverse effects in patients treated with moderate to high emotegenic and antidiarrheal protocol. Frequent symptoms like diarrhea, nausea, vomiting, stomatitis, abdominal pain and dyspepsia are comparatively assessed in patients undergoing different schedules of FOLFOX. Some rare symptoms i.e. constipation and dry mouth are also assessed in a similar manner.

Materials and Methods

The study designed in the Department of Pharmacology, University of Karachi was conducted in a leading cancer hospital in Pakistan, after institutional authorization, on the patients being admitted during 2008-2011, following informed patients consent. Inclusion criteria was

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maintained on the following ground; Clinically confirmed advanced colorectal carcinoma, Adequate blood count before therapy, Age 20-80 years, ECOG score of <3, Serum bilirubin <5× normal, Serum creatinine <135μmol/liter, Serum transaminases <×2.5 normal. Forty Eight patients were selected in the study as per defined criterion, among which thirty eight patients were assessable and evaluable by the end of the study. The patients with discontinued treatment before minimum of six cycles were excluded (n=5). The reasons for discontinued treatment range from patients noncompliance and/or severe hematological and non-hematological adverse reactions. Six patients withdrew from the study after few cycles of treatment as per offered choice.

The toxicity was graded according to CTC v2.0 on a scale of 1-5 according to the general grade definition of CTC v2.0. The sign and symptoms clearly associated with the disease and the disease progression are not graded during screening of treatment related toxicity. Similarly treatment delivery system malfunction is not graded during therapy related toxic screening. The defined parameters of gastrointestinal adverse effects in this study are diarrhea, stomatitis, nausea, vomiting, constipation and dry mouth, which were clinically evaluated after each treatment cycle in each treatment arm. The different combination regimens of oxaliplatin with 5FU/LV (FOLFOX), taken as investigational study protocols, with number of patients in each treatment arm, for toxicological screening were as follows

FOLFOX4 (n=13)

Oxaliplatin: 85 mg/m^2 IV on day 1

5-Fluorouracil: 400mg/m^2 IV bolus, followed by 600mg/m^2 IV continuous infusion for 22h on days 1 and 2

Leucovorin: 200mg/m^2 IV on days 1 and 2 as a 2-hour infusion before 5-Fluorouracil

(Cycle repeated on 2 weeks.)

FOLFOX6 (n=12)

Oxaliplatin: 100mg/m^2 IV on day 1

5-Fluorouracil: 400mg/m^2 IV bolus on day 1, followed by 2400mg/m^2 IV continuous infusion for 46h

Leucovorin: 400 mg/m^2 IV on day 1 as a 2-hours infusion before 5-Fluorouracil

(Cycle repeated every 2 weeks).

mFOLFOX6 (n=5)

Oxaliplatin: 100mg/m^2 IV 2h infusion on day 1

5Fluorouracil: 2000mg/m^2 IV continuous infusion on days 1 and 2 for 46h

Leucovorin: 100mg/m^2 2h infusion on day 1(cycle every 2 weeks up to 12 cycles).

FOLFOX7 (n=8)

Oxaliplatin: 130mg/m^2 IV on day 1

5-Fluorouracil: 2400mg/m^2 IV continuous infusion on days 1 and 2 for 46h

Leucovorin: 400 mg/m^2 IV on day 1 as a 2-hour infusion before 5-Fluorouracil

(Cycle repeated every 2 weeks).

Before doses, moderate to high emetogenic protocol is ensured. Supportive drugs for marrow depression (Nadir 10-14 days) was given with pegfilgrastim, filgrastim, epoetin alfa or/and darbepoeitin alfa. Antidiarrheal protocol was initiated by loperamide and/or diphenoxylate/ atropine sulfate. The cycles were repeated every 14 days (2 weeks) until disease progression. The frequency of grade 3 and grade 4 adverse effects were comparatively assessed with all toxicity grades by paired samples test. Data was analyzed on SPSS version 19 and comparative

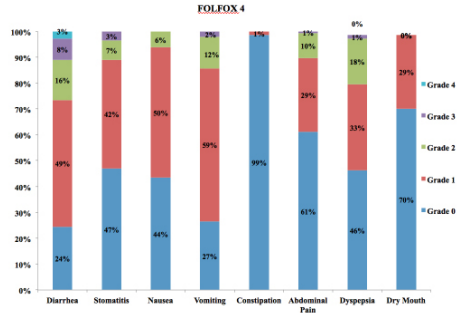

Figure 1. Percentage Frequency of Gastrointestinal Adverse Effects of all Toxicity Grades in FOLFOX4 Treatment Arm

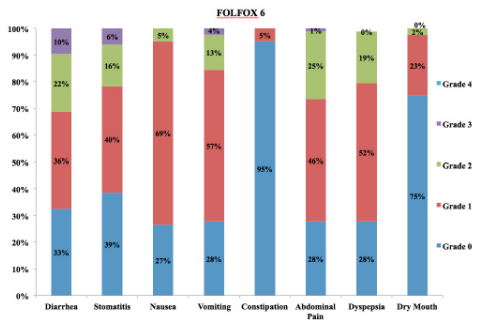

Figure 2. Percentage Frequency of Gastrointestinal Adverse Effects of all Toxicity Grades in FOLFOX6 Treatment Arm

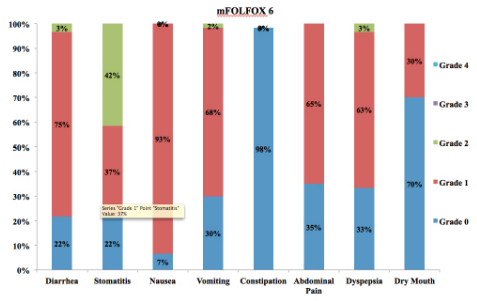

Figure 3. Percentage Frequency of Gastrointestinal Adverse Effects of All Toxicity Grades in mFOLFOX6 Treatment Arm

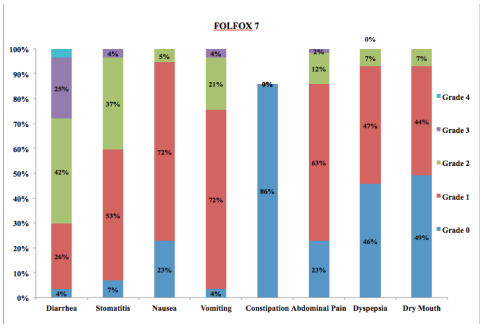

Figure 4. Percentage Frequency of Gastrointestinal Adverse Effects of all Toxicity Grades in FOLFOX7 Treatment Arm

assessment was made by one way ANOVA test. p value less than 0.05 is considered significant and less than 0.01 is considered highly significant, whereas a value less than 0.001 is considered very highly significant.

Results

Total number of cycles of FOLFOX 4 in all the evaluable and assessable patients was 147. The median number of cycle was 10, maximum number of cycles in any patient were 12 cycles. The most frequent adverse effect reported in the patients of FOLFOX 4 is vomiting (87) of grade 2. Grade 1 diarrhea was reported in 8% cases and Grade 2 was reported in 3% cases. The incidence rate and the toxicity grades of the symptoms with relative frequency are shown in Figure 1. The total number of cycles of FOLFOX 6 in the evaluable and assessable patients was 83.The median number of cycle was 6, maximum number of cycles in any patient were 8 cycles. The most frequent adverse symptom reported in the patients is nausea. Grade 3 diarrhea was reported in 10% patients of FOLFOX6 treatment arm. The total number of cycles of mFOLFOX 6 in all of the evaluable and assessable patients was 60. The most severe symptom reported in patients of mFOLFOX6 treatment arm is grade 2 stomatitis in 42% patients. There was no grade 3 or 4 GI toxicity in patients of mFOLFOX6 arm. The total number of cycles FOLFOX7 in all of the evaluable and assessable patients was 57. The median number of cycle were 8, maximum number of cycles in any patient were 09 cycles. The most frequent adverse symptom reported in the patients is nausea and vomiting (41) of grade 1 each. The most severe symptom reported in patients of FOLFOX7 treatment arm is grade 3 diarrhea in 25% patients and 4% grade 4 diarrhea.

The difference between the incidence rate of grade 1 and 2 toxicity and grade 3 toxicity of all parameters in GI toxicity is very highly significant (p<0.001). The difference between grade 1 and 2 incidence rate of constipation with grade 3 constipation is not significant (p=0.11). No grade 3 constipation was reported in any patient treated with FOLFOX. The difference between grade 3 GI toxicity with all grades of toxicity is shown in Table 1.

Table 1. Comparative Differences in Frequency of Grade 3 Gastrointestinal Adverse Effects with Grade 1 and Grade 2 Adverse Effects

Toxicity grades 1&2*3		Paired Samples Test					
		Mean	Std. deviation	Mean difference	t	df	p value
GI							
Diarrhea	1&2	6.026	3.46	5.132	7.545	37	0
	3	0.895	1.521				
Stomatitis	1&2	5.711	3.101	5.395	10.026	37	0
	3	0.316	0.962				
Nausea	1&2	6.421	3.561	6.421	11.115	37	0
	3	0	0				
Vomiting	1&2	6.789	2.905	6.579	13.051	37	0
	3	0.211	0.741				
Constipation	1&2	0.158	0.594	0.158	1.639	37	0.11
	3	0	0				
Abdominal Pain	1&2	5.184	3.279	5.105	9.674	37	0
	3	0.079	0.273				
Dyspepsia	1&2	5.395	3.259	5.342	10.084	37	0
	3	0.053	0.324				
Dry Mouth	1&2	2.895	3.278	2.895	5.444	37	0
	3	0	0				

Table 2. Comparative Differences in Frequency of Grade 4 Gastrointestinal Adverse Effects with All Grades of Toxicity

Toxicity Grade 1,2,3* Grade 4	Paired Samples Test					
	Mean	Std. deviation	Mean difference	t	df	p value
GI Diarrhea 1,2,3	6.921	3.316	6.763	12.133	37	0
Diarrhea 4	0.158	0.547				
Stomatitis 1,2,3	6.026	3.175	6.026	11.701	37	0
Stomatitis 4	0	0				
Nausea 1,2,3	6.421	3.561	6.421	11.115	37	0
Nausea 4	0	0				
Vomiting 1,2,3	7	2.885	7	14.956	37	0
Vomiting 4	0	0				
Constipation 1,2,3	0.158	0.594	0.158	1.639	37	0.11
Constipation 4	0	0				
Abdominal Pain 1,2,3	5.263	3.326	5.263	9.754	37	0
Abdominal Pain 4	0	0				
Dyspepsia 1,2,3	5.447	3.285	5.447	10.221	37	0
Dyspepsia 4	0	0				
Dry Mouth 1,2,3	2.895	3.278	2.895	5.444	37	0
Dry Mouth 4	0	0				

Table 3. Comparative Differences in Incidence Rate of Gastrointestinal Adverse Effects between Each Treatment Arm of FOLFOX

Toxicity		ANOVA	
		F	p value
GI	Diarrhea	5.162	0.005
	Stomatitis	4.02	0.015
	Nausea	4.941	0.006
	Vomiting	3.728	0.02
	Constipation	0.636	0.597
	Abdominal Pain	1.347	0.275
	Dyspepsia	1.952	0.14
	Dry Mouth	0.726	0.543

*p value < 0.05 (significant), p value < 0.01 (highly significant), p value < 0.001 (very highly significant)

The difference between the incidence rate of grade 1, 2 and 3 toxicity and grade 4 toxicity of all parameters in GI toxicity is very highly significant (p<0.001). The difference between grade 1, 2 and 3 incidence rate of constipation with grade 4 constipation is not significant (p=0.11). No grade 4 constipation was reported in any patient treated with FOLFOX. The difference between grade 4 GI toxicity with all grades of toxicity is shown in Table 2. The difference in the incidence rate of diarrhea among all treatment arms of FOLFOX is highly significant (p<0.01). The difference in the incidence rate of nausea among all treatment arms of FOLFOX is highly significant (p<0.01). The difference in the incidence rate of Stomatitis among all treatment arms of FOLFOX is significant (p<0.05). The difference in the incidence rate of all GI toxicities between FOLFOX 4, FOLFOX 6, FOLFOX 7 and mFOLFOX 6 is shown in Table 3.

Discussion

Gastrointestinal toxicities manifested by oxaliplatin based chemotherapy may be exacerbated by symptoms

of diarrhea, stomatitis, nausea, vomiting, abdominal pain, dyspepsia or dry mouth. Such toxicities directly alter the morbidity rate and quality of life in cancer patients undergoing chemotherapy (Najam et al., 2013). Therapeutic efficacy and toxicity differs according to doses, combinations schedules and route of administration (Bano et al., 2013d). GI toxicity is usually reported in the third or fourth week of first cycle of treatment and bowel wall injury is earlier in patients subjected to treatment with Oxaliplatin in combination with 5FU/LV, which indicates that oxaliplatin is the major contributor of GI toxicities (Kuebler et al., 2007). In the treatment arm FOLFOX 6 there were no reports of grade 4 diarrhea or stomatitis, however grade 3 diarrhea, stomatitis, vomiting and abdominal pain is reported. During our study, most symptoms were less than or equivalent to grade 2 toxicity, the difference in the incidence rate of grades 3 and 4 toxicities with all grades of toxicity is highly significant also reported earlier (Ramanathan *et.al*., 2003). The least severe reports of diarrhea among the four schedules of FOLFOX in our study were in mFOLFOX6 treatment arm. There were no reports of any adverse gastrointestinal toxicity of grade 3 or 4 in any patient. In our study there was a very high incidence rate of severe diarrhea in the patients treated with FOLFOX 7.

Severe diarrhea of grades 3 and 4 leads to many complications such as dehydration, paralytic ileus, hypokalemia, intestinal obstruction, metabolic acidosis or even renal toxicity. In case of severe mucositis/stomatitis, the chemotherapy is delayed or doses of Oxaliplatin are reduced until the neutrophil counts are recovered to an accepted level. It is important to correlate the GI adverse effects with the hematological parameters to correlate with neutropenia and thrombocytopenia and make the dose adjustment accordingly. In our study we encountered most cases with severity of symptoms in FOLFOX7 as compared to rest of the treatment schedules of FOLFOX and in context of gastrointestinal toxicity; we refer to modified FOLFOX6 as a comparatively safer choice. No gastrointestinal toxicity related death was encountered by us in any treatment arm; however deaths due to the severity of GI toxicity (enteropathy) have been reported earlier (Sharif *et al*., 2008). The most frequent and disturbing outcomes of GI toxicity in the patients of colorectal carcinoma subjected to different schedules of FOLFOX are diarrhea and stomatitis/mucositis. These two symptoms are also assigned to higher toxic grades in the patients. Both of these toxicities are known dose limiting toxicities manifested likewise in our experience. The standard dosing protocol of any FOLFOX schedule is inclusive of prophylactic agents for the management of diarrhea and stomatitis. These pretreatment prophylactic agents should never be overlooked, as this leads to treatment failure eventually as doses are interrupted, delayed and discontinued at a higher price inclusive of severe discomfort of diarrhea and stomatitis. We came across several patients' compliance issues and negligence that led to intricate scenarios. Patients should be made aware of the importance of prophylactic treatment of Stomatitis with antibacterial mouth wash, antifungal topical drugs i.e. nystatin, mucoprotective agents i.e. misoprostol/sucralfate etc. Patients should also be educated enough to be able to assess and report the severity of the symptoms.

In conclusion, the severity of gastrointestinal symptoms of toxicity was noted in FOLFOX7. The FOLFOX schedule can be effectively altered with mFOLFOX6 schedule with comparatively mild pattern of gastrointestinal toxicity keeping in consideration the multiple factors involved specially the treatment response in the patients with either schedule. We observed that the tilted safety efficacy ratio is in favor of the modified treatment schedule of FOLFOX6 in patients as far as the gastrointestinal adverse complications are concerned.

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