RESEARCH ARTICLE

Comparative Assessment of Skin and Subcutaneous Toxicity in Patients of Advanced Colorectal Carcinoma Treated with Different Schedules of FOLFOX

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Abstract

Objective: The study was designed to assess the skin and subcutaneous toxicity in patients with advanced colorectal carcinoma treated with four different schedules of FOLFOX. Methods: The patients with histologically confirmed advanced colorectal carcinoma (CRC) were included in the study as per specified inclusion criteria. Toxicity was graded according to CTC v2.0. The frequency of grade 3 and 4 adverse effects were comparatively assessed in each treatment arm. Results: Very severe toxicity was attributed to the FOLFOX7 schedule. The difference between the incidence rate of grade 4 toxicity with all other grades for all parameters of skin and subcutaneous toxicity was highly significant (p=0.00<0.001). Grade 4 hand and foot syndrome was reported only in the FOLFOX7 treatment arm. The most frequent adverse symptom of skin and subcutaneous toxicity reported in the patients treated with modified schedule of FOLFOX was pruritus (grade 1). Frequency and onset of skin and subcutaneous toxic symptoms like alopecia (p=0.000), nail discoloration (p=0.021) and pruritis (p=0.000) was significantly different in each FOLFOX treatment arm. A few cases of oncholysis were also reported in the FOLFOX7 treatment arm. Hand and foot syndrome was fast progressing in patients with grade 1 toxicity. Conclusion: Higher frequency and severity of hand and foot syndrome and pruritus wasa found in the FOLFOX7 treatment arm. Skin and subcutaneous toxicity was comparatively low in the FOLFOX6 treatment arm.

Keywords: FOLFOX - oxaliplatin - colorectal carcinoma - hand and foot syndrome - pruritis

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Introduction

Chemotherapy induced dermatological adverse effects are generalized rashes e.g. the rashes characterized of erythema multiforme and toxic epidermal necrolysis. Site-specific localized toxicity such as stomatitis, alopecia, extravasation reactions, nail disorders, or hand-foot syndrome (Wyatt, 2006).

Oxaliplatin and 5 Fluorouracil are frequently associated with hand and foot syndrome and hypersensitivity reactions (Eng, 2009), often leading to treatment disruption (Wehler et al., 2012). A platinum agent in combination with fluoropyrimidines is usually employed in metastatic disease setting (Kim et al., 2012), however the therapeutic efficacy and relative toxicity differs markedly in different doses, combinations, schedules of administration and routes of administration (Bano et al., 2012a) and is modulated by immediate or cumulative doses (Bano et al., 2012b). Hand and foot syndrome (HFS), also referred to as palmar-plantar erythrodysesthesia, is reported in patients treated with Oxaliplatin based schedules with and without 5FU (Zhang et al., 2012). Grade 1 hand and foot syndrome is reported in patients subjected to early chemotherapy with Oxaliplatin (130mg/m^2) after surgery (Yoshida et al., 2013). Hand and foot syndrome was characterized earlier by numbness and tingling, erythema associated with dysesthesia with and without paraestheisa. These symptoms would appear on the soles or the palms or sometimes on neck or chest or extremeties (Baack and Burgdorf, 1991). It is also reported that HFS is dose dependent and the probable mechanism is due to the accumulation of the drug in the skin (Bellmunt et al., 1988). HFS is associated with increase in number of eccrine glands on the palm and the soles, which are prone to cytotoxicity if the drug or its metabolite is bio-available in the sweat (Mrozek-Orlowski et al., 1999). HFS may be associated with increased temperature, pressure and vascularization of the surfaces of the hand and the feet (Lasserre and Hoff, 2004).

It is postulated that the keratinocytes (skin cells) has increased levels of thymidine phosphorylase leading to the accumulation of drug metabolite causing localized cytotoxicity (Asgari et al., 1999). The dermatological toxicities of 5FU which is the core component of FOLFOX regimen is known and accepted. These dermatological toxicities range from maculo-papular eruption,

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hyperpigmentation, to palmar-plantar erythrodysesthesia (PPES),which may be reversible upon discontinuation of therapy however the dosage and route of administration is also important (Leo et al., 1994). Concern is allotted to generate real consensus between oncologists and dermalogists to label and grade chemotherapy induced dermatological adverse effects (Duffour et al., 2010).

The skin and subcutaneous adverse effects are also related to allergic reactions. Incidence rate allergic reactions is 0.55% in patients of advanced colorectal carcinoma ,who had received oxaliplatin 2 hrs infusion in combination with 5FU/LV(Thomas et al., 2003).It is argued that Patients with severe allergic manifestations should not be rechallenged to oxaliplatin exposure even is if appropriate symptomatic management is given/planned (Polyzos et al., 2001), whereas other studies advocate that the re-challenge protocol is effective treatment opinion in patients implicated with hypersensitivity and treated with Oxaliplatin (Yanai et al., 2012). Cheng et al (2008), reported 25 (11 females and 14 males) cases of allergic reactions in a prospective study in patients receiving FOLFOX 4 for colorectal carcinoma. Ichikawa et al (2009), reported in a retrospective review of 105 patients subjected to FOLFOX chemotherapy, 16 cases of immediate allergic reaction and 9 cases of late allergic (identified by skin lesions) onset reactions (6.7% cases of grade 3 and 4). Leucovorin induced allergic reactions manifested as hives and flushing are also reported which are very rare (Damaske et al., 2012). Allergic cutaneous manifestations of Oxaliplatin can be complicated and aggravated (Bano et al., 2013a).

We have made an attempt to comparatively assess the frequency and severity of skin and subcutaneous toxicity in Pakistani patients treated with different schedules of FOLFOX as the toxicity of FOLFOX chemotherapy is implicated by ethnicity and genetic variability (Lee et al., 2013) and thus feature demarcations are evident from the globally reported data. Patients of colorectal carcinoma in Pakistan are presented with young age, subsided lesions but advanced stage of progressive disease, which caters to the severity of treatment induced adverse effects (Bano et al., 2013b).

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 maintained on the following grounds: 1) Histologically confirmed advanced colorectal carcinoma; 2) Adequate blood count before therapy; 3) Age 20-80 years; 4) ECOG score of <3; 5) No active gastric ulcer & gastrointestinal bleeding (since a year).

Forty five patients were initially included and 38 patients were assessable and evaluable by the end of the study. Three patients who had discontinued treatment before 6 cycles were excluded, one of the patient died due to disease complications whereas three patients withdrew from the study after first few treatment cycles as per offered choice. The distribution of the patients according to ethnicity/race in Pakistan is shown in Figure 1. 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 (e.g extravasation). The defined parameters of skin and subcutaneous toxicities in this study are Hand and foot syndrome, alopecia, nail disorder, dermatitis, rash erythematous, nail discoloration, oncholysis and pruritis, 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: 400 mg/m^2 IV bolus, followed by 600 mg/m^2 IV continuous infusion for 22 hours on days 1 and 2.

Leucovorin: 200 mg/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: 100 mg/m^2 IV on day 1.

5-Fluorouracil: 400 mg/m^2 IV bolus on day 1, followed by 2400 mg/m2 IV continuous infusion for 46 hours.

Leucovorin: 400 mg/m^2 IV on day 1 as a 2-hour infusion before 5-Fluorouracil (cycle repeated every 2 weeks).

mFOLFOX6 (n=5)

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

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

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

FOLFOX7 (n=8)

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

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

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 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

The total number of cycles of FOLFOX 4 in all the evaluable and assessable patients was 146. The median number of cycle were 10, maximum number of cycles in any patient were 12 cycles. The most frequent skin and subcutaneous adverse effect reported in the patients of FOLFOX 4 is grade 1 alopecia ensued by nail disorders The most severe symptom reported was hand and foot syndrome (3% grade 3 & 9% grade 2) in patients of FOLFOX4 (Figure 2A). The incidence rate of each symptom of skin and subcutaneous toxicity was assessed in 83 cycles of FOLFOX6. The median number of cycle was 6, maximum number of cycles in selected patient were 8 cycles. The most frequent adverse skin and subcutaneous symptom reported in the patients were nail disorders (grade 1) followed by alopecia (grade 1). The least frequently reported skin and subcutaneous adverse event was rash erythematous. The highest grade of symptoms was grade 3 and only symptoms reported with severity of grade 3 were Alopecia (6%), nail disorders (2%) and dermatitis (1%). The most frequent severe symptom reported was grade 1 nail disorders in 46% patients (Figure 2B). The total number of cycles of mFOLFOX 6 in the evaluable and assessable patients was 59.The median number of cycle was 12, maximum number of cycles in any patient were 12 cycles. There were no cases reported for rash erythmatous and oncholysis in mFOLFOX6 treatment arm. The most severe symptom reported in patients of mFOLFOX6 treatment arm is 10% grade 3 hand and foot syndrome (Figure 2C). There was no grade 4 skin and subcutaneous toxicity reported in patients of mFOLFOX6 arm. The total number of cycles in treatment arm FOLFOX7 were 56.The median number of cycle were 8, maximum number of cycles in any patient were 09 cycles. The most frequent symptom of skin and subcutaneous toxicity reported in the patients was alopecia (grade 1). The most severe symptom reported in patients of FOLFOX7 treatment arm is grade 3 hand and foot syndrome in 9% patients and 5% grade 4 hand and foot syndrome (Figure 2D). The difference between grade 3 skin and subcutaneous toxicity with all grades of toxicity is shown in Table 1. The difference between grade 4 skin and subcutaneous toxicity with

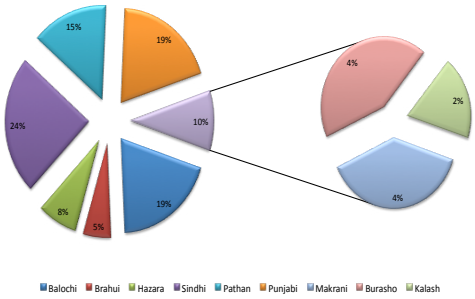

Figure 1. Percentage Distribution of Pakistani Patients According to Race/ethnicity

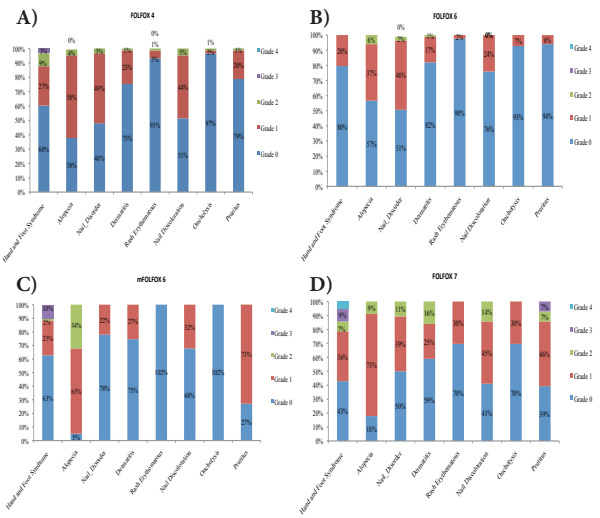

Figure 2. Percentage Frequency of Skin and Subcutaneous Adverse Effects of All Toxicity Grades. A) FOLFOX4 treatment arm, B) FOLFOX6 treatment arm, C) mFOLFOX6 treatment arm and D) FOLFOX7 treatment arm

Table 1. Grade 3 Toxicity Compared to Grade 1 and Grade 2 Toxicity

Toxicity	Mean	Std. Deviation	Mean Difference	t	df	p value
Skin and Subcutaneous						
Hand and Foot Syndrome 12	2.895	2.759	2.474	5.256	37.000	0.000
Hand and Foot Syndrome 3	0.421	1.328				
Alopecia 12	6.026	3.507	6.026	10.594	37.000	0.000
Alopecia 3	0.000	0.000				
Nail Disorder 12	4.132	3.379	4.132	7.538	37.000	0.000
Nail Disorder 3	0.000	0.000				
Dermatitis 12	2.368	3.529	2.368	4.137	37.000	0.000
Dermatitis 3	0.000	0.000				
Rash Erythematous 12	0.763	1.777	0.763	2.647	37.000	0.012
Rash Erythematous 3	0.000	0.000				
Nail Discoloration 12	3.763	3.166	3.763	7.327	37.000	0.000
Nail Discoloration 3	0.000	0.000				
Oncholysis 12	0.737	1.766	0.737	2.572	37.000	0.014
Oncholysis 3	0.000	0.000				
Prutitus 12	2.895	3.798	2.789	4.508	37.000	0.000
Prutitus 3	0.105	0.509				

Table 2. Grade 4 Toxicity Compared to All Toxicity Grades

Toxicity	Mean	Std. Deviation	Mean Difference	t	df	p value
Skin and Subcutaneous						
Hand and Foot Syndrome 123	3.316	3.214	3.237	6.123	37.000	0.000
Hand and Foot Syndrome 4	0.079	0.487				
Alopecia 123	6.026	3.507	6.026	10.594	37.000	0.000
Alopecia 4	0.000	0.000				
Nail Disorder 123	4.132	3.379	4.132	7.538	37.000	0.000
Nail Disorder 4	0.000	0.000				
Dermatitis 123	2.368	3.529	2.368	4.137	37.000	0.000
Dermatitis 4	0.000	0.000				
Rash Erythematous 123	0.763	1.777	0.763	2.647	37.000	0.012
Rash Erythematous 4	0.000	0.000				
Nail Discoloration 123	3.763	3.166	3.763	7.327	37.000	0.000
Nail Discoloration 4	0.000	0.000				
Oncholysis 123	0.737	1.766	0.737	2.572	37.000	0.014
Oncholysis 4	0.000	0.000				
Prutitus 123	3.000	3.848	3.000	4.805	37.000	0.000
Prutitus 4	0.000	0.000				

Table 3. Difference in Toxic Parameters between Each Treatment Arm of FOLFOX

Toxicity		ANOVA	
		F	p value
Skin & Subcutaneous	Hand and Foot Syndrome	2.475	0.078
	Alopecia	15.859	0.000
	Nail Disorder	1.905	0.147
	Dermatitis	0.585	0.629
	Rash Erythematous	2.631	0.066
	Nail Discoloration	3.701	0.021
	Oncholysis	2.437	0.082
	Prutitus	10.667	0.000

all grades of toxicity is shown in Table 2.There was no difference in the pattern of all grades of adverse effects like hand and foot syndrome ,nail disorders, dermatitis ,rash erythematous and oncholysis between the different schedules of FOLFOX. The frequency and onset of skin and subcutaneous toxic symptoms like alopecia (p=0.000), nail discoloration (p=0.021) and pruritis (p=0.000) was significantly different in each treatment arm of FOLFOX (Table 3).

Discussion

Hand and foot syndrome was the only symptom of skin and subcutaneous toxicity of Grade 3 in FOLFOX4 (Figure 2A). Such conditions, even mild, should be managed from the beginning as it can progress and complicate within a very short span of time without treatment. Use of topical creams and emollients is very effective for grade 1 HFS (Gerbrecht, 2003). A regular application of topical petroleum-lanolin ointment base with hydroxyquinolone sulphate three times per day was rendered effective, also reported by Chin et al. (2001). Topical corticosteroids have an effective role in the management of symptoms however these may also cause thinning of the skin (Komamura et al., 1995; Vakalis et al., 1998), which was observed in some female patients in our study. The patients were also prescribed with Vitamin B6, which is known to be highly effective in both the prophylaxis and control of symptoms (Fabian et al., 1990). Other than HFS, there were no other symptoms of grade 3 in the patients of FOLFOX 4 pertaining to skin and subcutaneous toxicity (Figure 2A). The least frequent reported adverse affect on skin and subcutaneous category in FOLFOX4 were rash erythmatous 6% and oncholysis 3%. Grade 1 alopecia (58%) and nail discoloration (44%) was commonly experienced by patients in FOLFOX4 treatment arm. Nail disorders (49% grade 1) other than discoloration or oncholysis were pitting (psoriasis), brittle nails, clubbing, white nails/spoon nails due to anemia or iron deficiency etc.

Grade 3 and 2 hand and foot syndrome was not reported in FOLFOX 6 treatment arm, whereas 20% grade 1 hand and foot syndrome was reported. The least reported adverse manifestation of skin and subcutaneous toxicity is 2% grade 1 rash erythmatous in FOLFOX6 treatment arm (Figure 2B). The incidence and frequency of skin and subcutaneous toxicity in FOLFOX6 treatment arm is comparatively less in patients with FOLFOX 4 treatment arm. Mild hypersensitivity reactions with Oxaliplatin are usually self limiting but may be pronounced after repeated exposures (Najam et al. 2012).

Pruritis (grade 1) is the most frequently reported symptom in modified FOLFOX6 as compared to the rest of the parameters of skin and subcutaneous toxicity (Figure 2C). Rash erythmatous and oncholysis were not reported in any patient during 12 cycles of treatment with mFOLFOX6 (Figure 2C). One of the limitations of this finding is the limited number of cycles (59 cycles of treatment) in modified FOLFOX6 treatment arm. The propensity of allergic reactions with platinum compounds lies with the increased number of cycles during chemotherapy, as even 27% incidence rate of allergic reactions was reported in patients who received more than seven cycles of treatment (Shlebak et al., 1995; Markman et al., 1999; Polyzos et al., 2001). Platinum compounds can induce direct cytotoxicity by generation of superoxide radicals besides formation of DNA crosslinks and monofunctional and bifunctional adducts (Bano et al., 2013c).

Rash Erythematous and oncholysis are the least frequently reported symptoms of skin and subcutaneous toxicity in FOLFOX 4, FOLFOX6 and modified FOLFOX6, whereas a high incidence rate of both these troublesome manifestations of skin and subcutaneous toxicity is reported in FOLFOX7 (Figure 2D). Moreover the most severe cases of grade 4 hand and foot syndrome is reported only in patients of FOLFOX7, whereas grade 4 hand and foot syndrome was not reported in any other treatment arms. Our data leads us to conclude that FOLFOX7 is the most toxic schedule for skin and subcutaneous regions. Most of the patients affected by hand and foot syndrome are presented with the clinical symptoms of dysesthesia with tingling pain on the palms and the soles. The condition progresses over a couple of days and leads to a more painful condition characterized by burning pain associated with erythema and symmetric swelling (Lassere and Hoff, 2004). The palms of the hands are more commonly affected rather than the soles. Erythema does not frequently occur in areas except the soles and the palms but there are reports of mild erythema or morbiliform eruption associated with acral response on the neck, chest, trunk or the extremeties (Baack et al., 1991). HFS may cause blistering and shedding of the skin on continued exposure of the causative agent. The symptoms of HFS may disappear or reverse upon discontinuation of therapy with appropriate management protocol such as pyridoxine (Van custem et al., 2000; Lauman and Mortimer, 2001) steroids and dimethysulfoxide 99% (Lopez et al., 1999).The condition gives way to complications like infections or septicemia if it is severe and not managed properly. The performance status of the patient is impaired when HFS is associated with pain, blistering, ulceration and moist desquamation (shedding/scaling) and hence requires appropriate management to avoid complications (Jucgla and Sais, 1997).

Table 1 shows that grade 3 skin and subcutaneous toxicity is manifested as hand and foot syndrome and pruritis in patients subjected to different treatment

schedules of FOLFOX. Table 2 shows that Grade 4 skin and subcutaneous toxicity is not frequent in patients subjected to FOLFOX4. Few cases of Grade 4 hand and foot syndrome is reported in FOLFOX7. A similar study reported that, prolongation of the infusion time of Oxaliplatin also allows continuation of the therapy despite allergic manifestations (Schüll et al., 2001), recurrence of the allergy within 3 cycles of chemotherapy when the patients were rechallenged (Ichikawa et al., 2009). Table 3 shows that the pattern of skin and subcutaneous toxicity such as alopecia and pruritus is dissimilar between different schedules of FOLFOX. Pruritis is less frequently reported in patients of FOLFOX6 treatment arm whereas the most cases of pruritus were reported in modified schedule of FOLFOX6. Similarly the adversity of pruritus was most severe in few patients of FOLFOX7 treatment arm. Similarly alopecia was more frequently reported in FOLFOX7 treatment arm and least frequently reported in FOLFOX6 treatment arm. The toxicity in FOLFOX6 treatment arm is less due to less number of cycles, even though higher doses as compared to FOLFOX4, which is indicative of the significance of toxicity pertaining to cumulative dose of Oxaliplatin or 5FU and repeated exposures.

In conclusion: Hand and foot syndrome is a debilitating condition, adversely affecting the performance status in patients who experience the severity of this symptom. The most severe hand and foot syndrome are presented in patients of FOLFOX 7.Comparatively less intense symptoms were reported in both FOLFOX4 and mFOLFOX6 treatment arms. Hand and foot syndrome was less frequent and comparatively mild in patients of FOLFOX6 treatment arm. Besides topical management of the condition, the important thing is to enable the patient to identify and report the progression of this symptom, as this adverse condition appears to be mild in the beginning and if not addressed properly, complicates within a very short time span. Rash erythmatous and oncholysis are rarely reported in any other FOLFOX schedule but few cases of both these toxicity are reported in patients of FOLFOX7. Pruritus was most frequently reported in the patients of modified FOLFOX6; nearly double the incidence rate of pruritis is reported in modified schedule of FOLFOX6 as compared to FOLFOX4.

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