Original Article

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Comparative Study of Folfox 4 Versus Capeox Chemotherapy Regimens in Adjuvant Therapy and Metastatic Colorectal Cancer

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Abstract

Introduction: Adjuvant chemotherapy is considered the standard of care for patients with colorectal cancer after curative resection. Studies on adjuvant and metastatic colorectal cancer showed FOLFOX4 and CAPEOX are equal in efficacy (Progression free survival (PFS), OS) but differ in terms of Toxicity and Compliance. *Aims:* The present study is aimed to compare the toxicity and compliance between FOLFOX4 and CAPEOX in adjuvant and metastatic colorectal cancer. *Materials and Methods:* Prospective randomized comparative study of patients with adjuvant and metastatic colorectal cancer who are histopathologically confirmed colorectal malignancy with high risk Stage II, Stage III, Stage IV Colorectal cancer. *Results:* The baseline characteristics between the two groups were comparable in almost all aspects. Incidence of grade 3 (41.4% v 7%) and grade 4 (20.7% v 0%) neutropenia were higher with FOLFOX4 arm as compared to the CAPOX arm which showed a statistical significance (p=0.000). As compared to the FOLFOX4 arm, CAPOX arm showed a higher incidence of grade 2 (51.2% v 0%) and grade 3 (27.9% v 0%) hand foot syndrome (HFS) which is statistically significant (p=0.000). Dose limiting toxicities (DLTs) were seen with 95.3% patients in the CAPOX arm and 96.6% patients in the FOLFOX4 arm. Patients in the CAPOX arm showed a higher compliance rates (CAPOX 60.5%, FOLFOX4 31%) than patients in the FOLFOX4 arm with a statistical significance (p=0.014). *Conclusion:* The overall grade 3 and 4 toxicity is significant with FOLFOX4 arm as compared to CAPOX arm. CAPOX arm isassociated with a higher incidence of grade 2 & 3 hand foot syndrome (HFS), Patients who received CAPOX showed a better compliance to treatment as compared to patients who received FOLFOX4.

Keywords: Infusional 5-Floro Uracil (FOLFOX4); Capecitabine (CAPOX); Colorectal cancer (CRC).

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Introduction

Colorectal cancer (CRC) is an ever growing global public health concern. CRC is a heterogeneous disease that occurs in the colon and the rectum, parts of the gastrointestinal system. The colon has 4 sections; the ascending, transverse, descending, and sigmoid colon, and the latter is where most CRC arise. The majority of CRC develop slowly from adenomatous polyps or adenomas. Although surgical resection is potentially curative, local or distant recurrences develop in many patients.[1] Delivering adjuvant chemotherapy to patients with high-risk Stage II and Stage III colon cancer has been associated with improvement in overall survival (OS) compared with surgery alone. The use of oxaliplatin in combination with either IV 5-fluorouracil (5-FU) and leucovorin (LV) or Oral capecitabine has decreased the risk of recurrence in high risk Stage II and Stage III disease.[2] The gold-standard treatment for patients with rectal cancer

(Stage II and III) is either traditional way of surgery followed by radiotherapy and chemotherapy or currentstrategy of preoperative combined fluoropyrimidine-based chemoradiotherapy followed bysurgery and adjuvant chemotherapy.[3] Systemic therapy is the mainstay of management for patients with metastatic CRC (mCRC). The systemic treatment of mCRC involves the use of active cytotoxic drugs and biological agents either in combination or as single agents. Tomaximize outcome, patient should receive oxaliplatin, irinotecan, and either 5-FU or Capecitabine at some point during the course of treatment. Prolonged infusion of LV/5FU has an improved safety and efficacy profile compared with the bolus LV/5FU, butthe inconvenience and morbidity associated with long term central/peripheral venous access emphasized the need for alternative regimens. Oral formulations of fluoropyrimidines were designed to reduce the discomfort and morbidity & to mimic the effects of continuous infusion 5-FU. Capecitabine is a third-generation prodrug designed as a precursor to 5'-deoxy-5-fluorouridine (doxifluridine), which is selectively activated by tumor cells to 5-FU. Studies on adjuvant and metastatic colorectal cancer showed FOLFOX4 and CAPEOX are equal in efficacy (Progression free survival (PFS), OS) but differ in terms of Toxicity and Compliance. Till to date, Compliance has not been studied in any of the randomized controlled trials done between FOLFOX4 and CAPEOX. The present study is aimed to compare the toxicity and compliance between FOLFOX4 and CAPEOX in adjuvant and metastatic colorectal cancer.

Materials and Methods

Prospective randomized comparative study patients of adjuvant and metastatic colorectal cancerwho presented to the Medical Oncology Out-patient Department, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati during the period between June '15 and April '16 were included in the study.

Inclusion criteria

Histopathologically confirmed colorectal malignancy, Patients with high risk Stage II, Stage III, Stage IV Colorectal cancer

Exclusion criteria

Patients with progressive/recurrent disease, Stage I, Stage II disease except those with high risk features, performance status ECOG ≥ 3 and Pregnancy

Patient Characteristics

Patients with performance status ECOG 0–2. Patients with Hemogram within the following limits

a. Hb>8g/dl
b. WBC greater than 3,000/mm^3,
c. Absolute neutrophil count greater than 1,500/mm^3,
d. Platelet count greater than 100,000/mm^3

Biochemical profile within normal limits. The study was started after getting clearance by the Institutional Ethical Committee. After taking a written informed consent all the patients were subjected to a thorough clinical evaluation and all the data were documented in a Data Collection Sheet including age, sex, comorbidities, symptoms and signs, performance status (ECOG), tumour type & stage, histology, specific anticancer therapy received in past 2 months (surgery, chemotherapy, radiotherapy), operative details and postoperative HPE, Tumor marker levels (CEA), Imaging findings and data regarding the specific toxicity and patient compliance to the treatment.

After randomisation (Block method), all patients were planned for chemotherapy (adjuvant/ metastatic) to one of the chemotherapy arms, either FOLFOX4 or CAPOX arm for 6 months. After allotment of study patients to one of the treatment arms (FOLFOX4 or CAPEOX), Toxicity (Haematological, Non Haematological) between the treatment arms was assessed by using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Compliance for the treatment (FOLFOX4 or CAPEOX) was assessed by interviewing the eligible patients with questions addressing the capecitabine use in terms of number of tablets per day, dose per day, no of days received per cycle as per schedule and causes for failing doses of capecitabine in each cycle and by objective assessment of time interval between the cycles and causes for failing or delay in cycles in both the arms.

A follow up period of 28 days after the last cycle is recommended as per study design. Database were updated regularly according to the clinical information available on scheduled oncologic visits, hospital admissions, electronic health records and/ or telephone calls if necessary.

Data were recorded on a predesigned Data Collection Sheet and managed using Microsoft Excel 2007 (Microsoft Corp, Redmond, WA). All the

entries were double checked for any possible error. The collected data were analysed with IBM. SPSS statistics software 23.0 Version. Statistical tools the probability value (*p*-value) 0.05 is considered as a significant.

Results

A total of 110 eligible patients were included in the study with fifty five patientsin each arm. Twelve patients in the CAPEOX arm and twenty sixin the FOLFOX4 are defaulted and did not complete the planned treatment schedule and were excluded from the study. 43 patients in the CAPEOX arm and 29 patients in the FOLFOX4 arm completed the intended treatment and were eligible for evaluation and analysis.

The baseline characteristics between the two groups were comparable in almost all aspects. None of the patients in FOLFOX4 arm and 7% in the CAPOX arm were in the age group of >70 yrs. 83.7% patients in the CAPOX arm and 72.4% in the FOLFOX4 arm had an ECOG performance status of 1. Carcinoma rectum accounted for approximately

Table 1: Baseline patient characteristics

Patient details	CAPOX, *n*=43	FOLFOX4, *n*=29	*p*-values
	No. (%)	No. (%)	
Age in yrs			
<50	19 (44.2%)	15 (51.7%)	*p*=0.327
50–70	21 (48.8%)	14 (48.3%)	
>70	3 (7%)	0 (0%)	
Sex			
Males	22 (51.2%)	15 (51.7%)	*p*=0.963
Females	21 (48.8%)	14 (48.3%)	
PS			
0	0 (0%)	0 (0%)	*p*=0.247
1	36 (83.7%)	21 (72.4%)	
2	7 (16.3%)	8 (27.6%)	
Diagnosis			
Anorectum	2 (4.7%)	1 (3.4%)	*p*=0.715
Ascending colon	5 (11.6%)	4 (13.8%)	
Caecum	7 (16.3%)	1 (3.4%)	
Hepatic flexure	1 (2.3%)	1 (3.4%)	
Rectosigmoid	6 (14%)	6 (20.7%)	
Rectum	14 (32.6%)	8 (27.6%)	
Sigmoid colon	6 (14%)	6 (20.7%)	
Splenic flexure	2 (4.7%)	1 (3.4%)	
Transverse colon	0 (0%)	1 (3.4%)	
Histology			
WD Adenoca	5 (11.6%)	3 (10.3%)	*p*=0.777
MD Adenoca	33 (76.7%)	24 (82.8%)	
PD Adenoca	5 (11.6%)	2 (6.9%)	
T Stage			
T3	17 (39.5%)	14 (48.3%)	*p*=0.537
T4a	12 (27.9%)	9 (31%)	
T4b	14 (32.6%)	6 (20.7%)	
N Stage			
N0	22 (51.2%)	13 (44.8%)	*p*=0.316
N1	14 (32.6%)	13 (44.8%)	
N2a	0 (0%)	1 (3.4%)	
N2b	7 (16.3%)	2 (6.9%)	
Stage			
IIA	5 (11.6%)	3 (10.3%)	*p*=0.082
IIB	4 (9.3%)	4 (13.8%)	
IIC	2 (4.7%)	2 (6.9%)	
IIIB	6 (14%)	12 (41.4%)	
IIIC	8 (18.6%)	3 (10.3%)	
IV	18 (41.9%)	5 (17.2%)	
Adjuvant	25 (58.1%)	24 (82.8%)	
Metastatic	18 (41.9%)	5 (17.2%)	

30% in each group. Moderately differentiated adenocarcinoma is seen in 76.7% patients in CAPOX arm and 82.8% patients in the FOLFOX4 arm. Approximately 50% were node positive in both the groups. Among the total study population, 49 patients (CAPOX 25, (58.1%) and FOLFOX4 24, (82.8%)) were on adjuvant basis whereas remaining 23 were on palliative intent (CAPOX 18, (41.9%) and FOLFOX4 5, (17.2%)) (Table 1).

Incidence of Grade 3 (41.4% v 7%) and Grade 4 (20.7% v 0%) neutropenia were higher with FOLFOX4 arm as compared to the CAPOX arm which showed a statistical significance (p=.000). FOLFOX4 arm reported a higher incidence of febrile neutropenia (34.5% v 2.3%) as compared to the CAPOX arm which showed a statistical significance (p=.000) (Fig. 1).

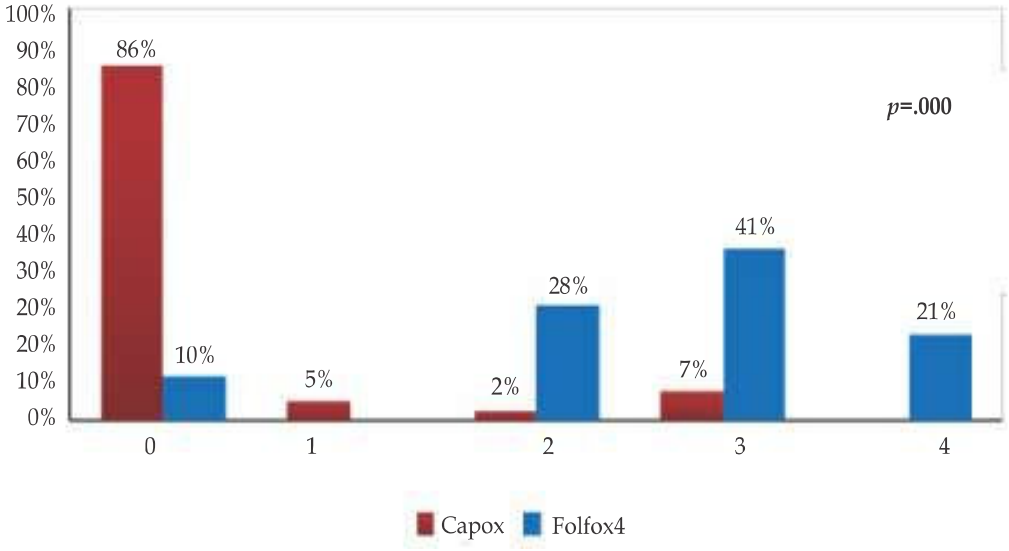

Fig. 1: Incidence of Neutropenia by grade

CAPOX arm showed a higher incidence of Grade 1 thrombocytopenia (34.9% v 10.3%) as compared to the FOLFOX4 arm with a statistical significance (p=.035) (Fig. 2).

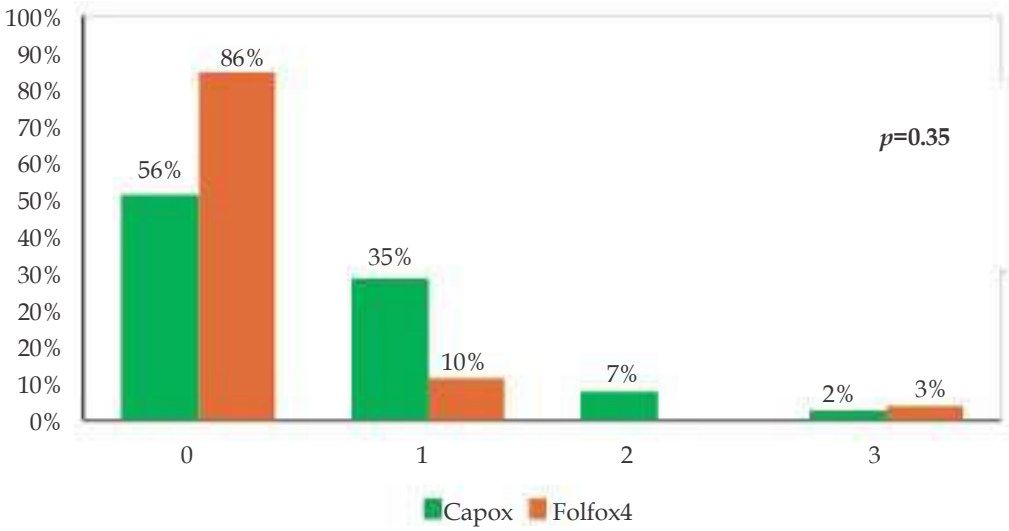

Fig. 2: Incidence of Thrombocytopenia by grade

A high incidence of Grade 2 anemia is reported with both groups with a rate of 41.4% with FOLFOX4 arm and 27.9% with CAPOX arm which showed a statistical non-significance (p=.108) (Fig. 3).

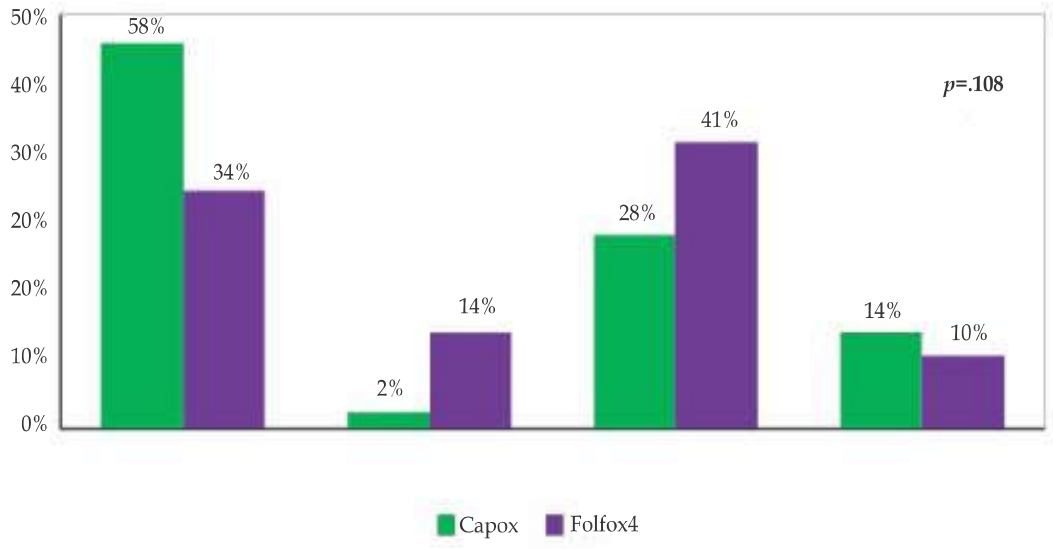

Fig. 3: Incidence of Anemia by grade

As compared to the FOLFOX4 arm, CAPOX arm showed a higher incidence of Grade 2 (51.2% v 0%) and Grade 3 (27.9% v 0%) hand foot syndrome (HFS) which is statistically significant (p=.000) (Fig. 4).

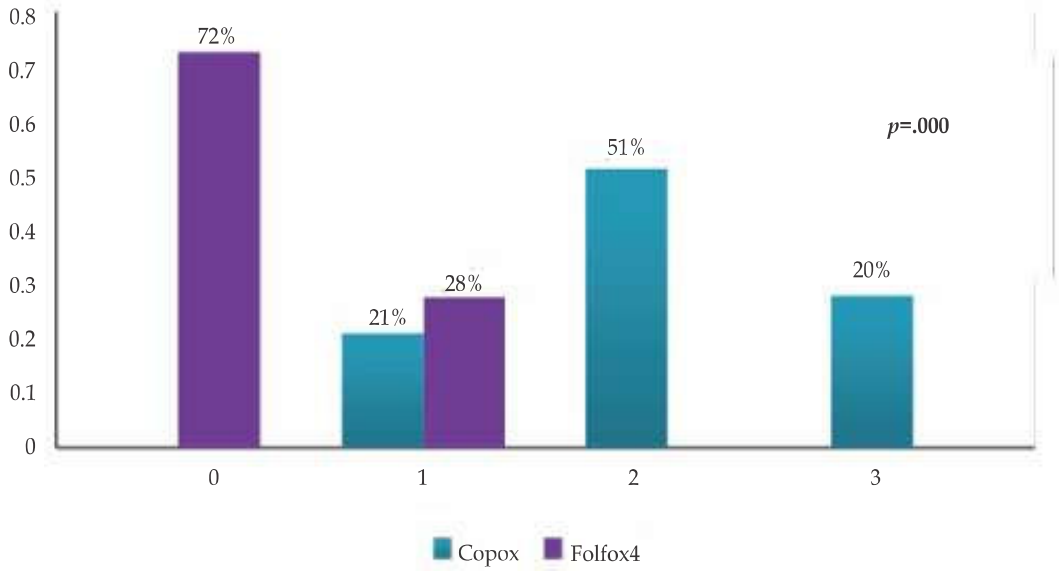

Fig. 4: Incidence of HFS by grade

Grade 1 vomiting is higher with CAPOX arm (60% v 24%) as compared to the FOLFOX4 arm which is statistically significant (p=.004) whereas Grade 3 vomiting is higher with FOLFOX4 arm (31% v 12%) which showed a statistical non-significance (p=.098) (Fig. 5).

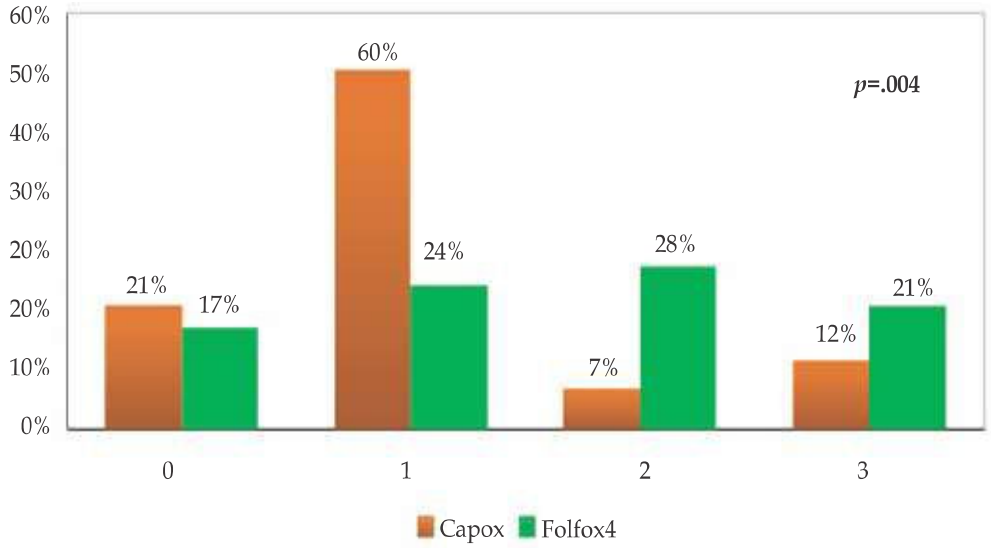

Fig. 5: Incidence of vomiting by grade

A higher incidence of Grade 3 diarrhea (58.6% v 44.2%) is reported with FOLFOX4 arm as compared to the CAPOX arm which is statistically non-significant (p=.190). All patients in the CAPOX arm had some diarrhea whereas 6.9% patients in the FOLFOX4 arm did not experience diarrhea (Fig. 6).

The nausea rates were comparable (CAPOX 20.9%, FOLFOX4 17.2%) between the two groups with no statistical significance (p=.698).

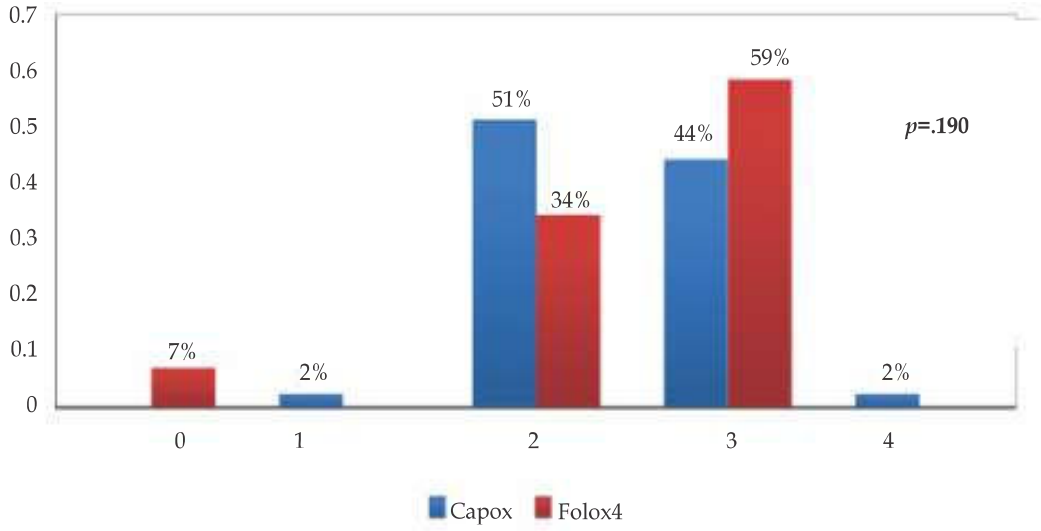

Fig. 6: Incidence of diarrhea by grade

Fifteen point one percent patients in the FOLFOX4 arm reported a Grade 3 peripheral neuropathy as compared to the 12.3% patients in the CAPOX arm which is statistically non-significant (p=.933) (Fig. 7). Fatigue is observed in all patients (100%) with FOLFOX4 arm as compared to the 90.7% patients with CAPOX arm with no statistical significance (p=.143).

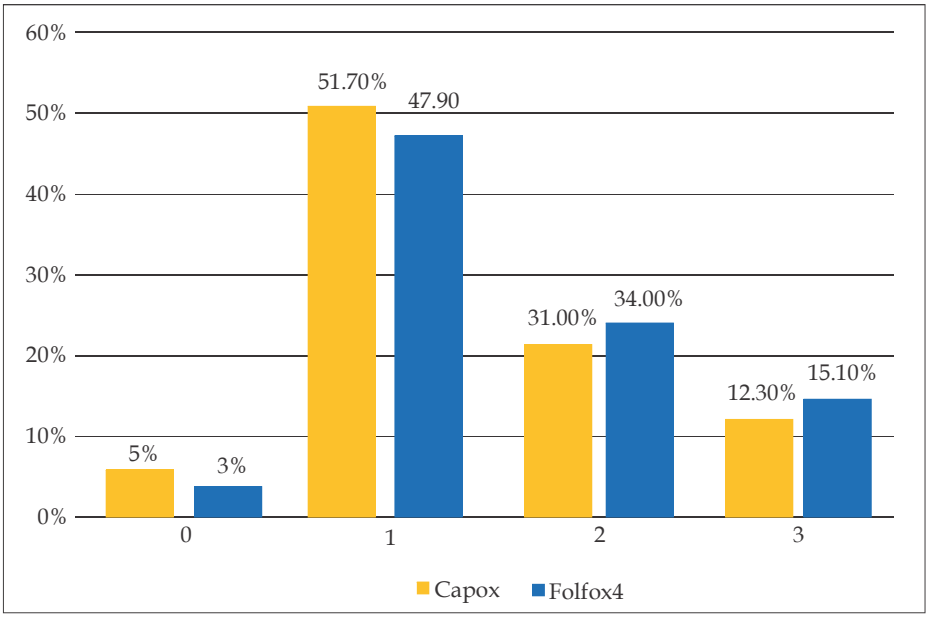

Fig. 7: Incidence of Peripheral neuropathy by grade

Dose limiting toxicities (DLTs) were seen with 95.3% patients in the CAPOX arm and 96.6% patients in the FOLFOX4 arm. The dose limiting toxicities such as diarrhea (CAPOX 37.2%, FOLFOX4 13.8%, *p*=.035), HFS (CAPOX 37.2%, FOLFOX4 0%) and myelosuppression (CAPOX 2.3%, FOLFOX4 51.7%) between the two arms showed a statistical significance (*p*=.000) whereas fatigue (CAPOX 2.3%, FOLFOX4 6.9%), peripheral neuropathy (CAPOX 14%, FOLFOX4 20.7%) and vomiting (CAPOX 2.3%, FOLFOX4 3.4%) did not show a statistical significance (Fig. 8).

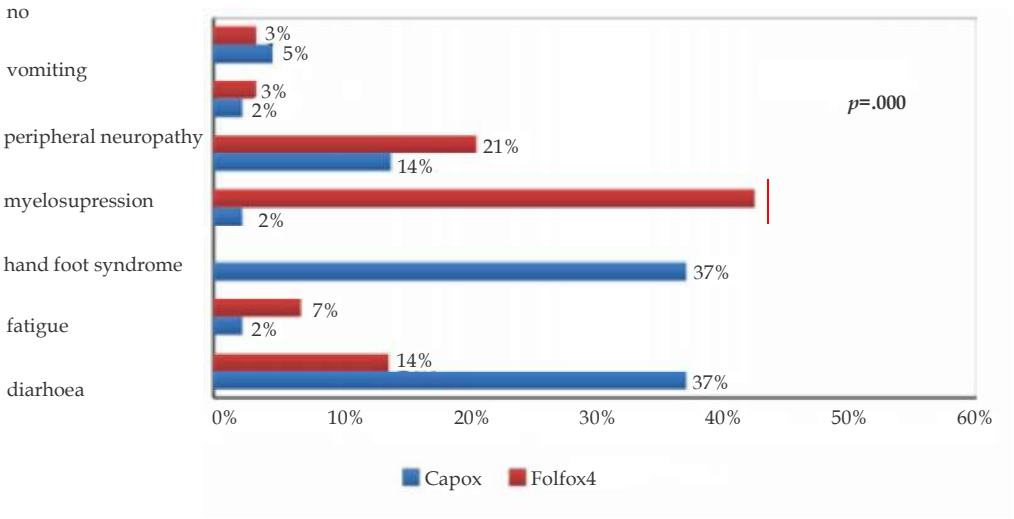

Fig. 8: Dose limiting toxicities

Out of the 71.4% females, only 52.4% of them were received the planned 2500 mg/day (5 tablets) and showed a compliance to treatment whereas the remaining 19% of the patients received a lesser dose of 4 tablets/day and were non-compliant (Fig. 9).

Out of the 50% males, only 41% of them were received the planned dose of 3000 mg/day (6 tablets) which showed a compliance whereas the

remaining 9% of the patients received a lesser dose and were non-compliant. Similarly, out of the 27% males, 14% of them were received the planned 3500 mg/day (7 tablets) with remaining 13% of them were showed a noncompliance to the treatment.

The mean number of days of capecitabine received is 12.09 days with a range of 5–14 days. The average delay in between the cycles is (CAPOX 4.84 days, FOLFOX4 8 days) with a statistical significance of (p=0.001).

Based on the above descriptive, for each patient in two groupsa status of treatment compliant or noncompliant was assigned. Most of the noncompliance to treatment was due to the toxicities of the particular regimen. Incidence of peripheral neuropathy and HFS were not interfering with the compliance in both arms, except for dose reductions.

Patients in the CAPOX arm showed a higher compliance rates (CAPOX 60.5%, FOLFOX4 31%) than patients in the FOLFOX4 arm with a statistical significance (p=.014). Overall and within each group, the compliance between males and females is statistically non-significant. Between the age groups (<50 yr, 50–70, >70 yr) compliance is statistically significant in the overall study population (p=0.018) & in the CAPOX arm (p=0.012). In FOLFOX4 arm it is statistically non-significant.

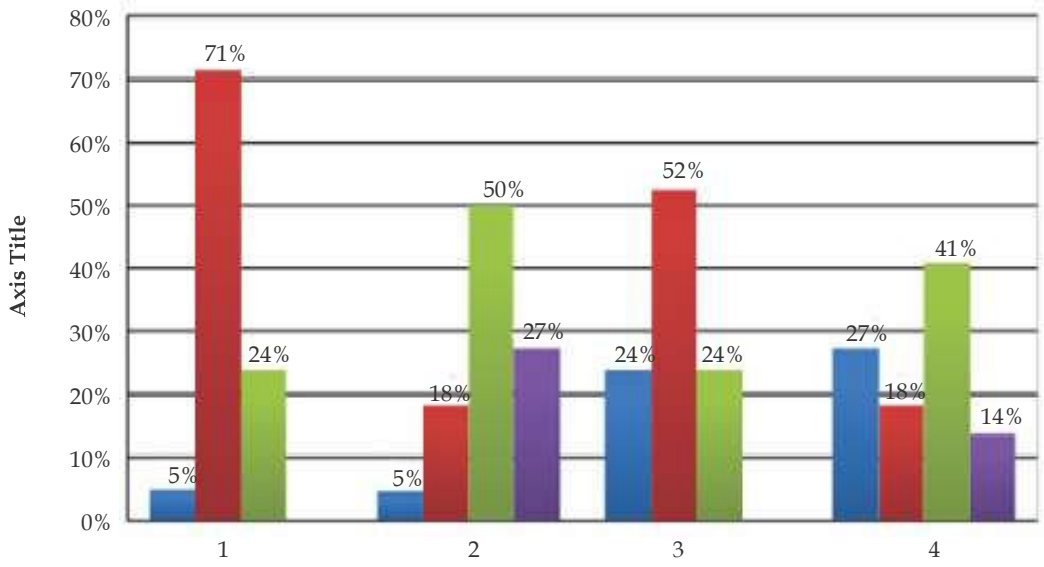

Fig. 9: Capecitabine dose/number of tablets planned & received/day

Discussion

In the present study, patients with high risk Stage II to Stage IV colorectal cancer were randomized between FOLFOX4 and CAPOX arms, which are two established chemotherapy regimens with similar efficacy (PFS, OS) but distinct toxicity profiles.

The median age of patients in this study in FOLFOX4 arm is 50 yrs and in CAPOX arm is 52 yrs. which is a decade earlier than the median age of patients in the study reported by Jim Cassidy *et al.*[4] which reported a median age of 62 yrs. in the FOLFOX4 arm and 61 yrs. in the CAPOX arm. Another study by Vicky C Tse *et al.*[5] also reported a median age at diagnosis of 61.9 yrs. in the FOLFOX4 arm and 63.9 yrs. in the CAPOX arm. Similarly, a study reported by Yoshihito ohhara *et al.*[6] also reported a median age of 60 yrs. with both FOLFOX4 and CAPOX arms. The difference in the median age of diagnosis in the present study compared with other studies was explained by the fact that colorectal cancer is generally a disease affecting the individuals 50 years of age or older in both Indian and western settings as reported by the Kenneth R *et al.*,[7] Laishram RS *et al.*[8] and a study by the Rasool S *et al.*[9]

The present study showed a distribution of 51.7% males & 48.3% females in the FOLFOX4 armand 51.2% males & 48.8% females in the CAPOX arm which is different from the distribution of the 64% males & 36% females in the FOLFOX4 arm and 61%

males & 39% females in the CAPOX arm reported by the Jim Cassidy study *et al.* but comparable to the study reported by Yoshihito ohhara *et al*[6] which showed a distribution of 48% males & 52% females in FOLFOX4 arm and 58% males & 42% females in the CAPOX arm. 72.4%patients in the FOLFOX4 arm and 83.7% in the CAPOX arm had an ECOG PS of 1 which is in contrast to the Yoshihotoohhara study *et al.*[6] which showed the majority of patients had an ECOG PS of 0 (FOLFOX4 99%, CAPOX 95%) but comparable to the Jim Cassidy study *et al.*[4] and Vicky C Tse *et al.*[5] where the majority of them had an ECOG PS of 1.

The distribution of primary tumor site is comparable with the study by Jim Cassidy *et al.*[4] where approximately 70% of cases were colon and remaining were rectal cancers. Another study by Yoshihoto *et al.*[6] also showed the similar distribution of primary site.

The present study showed a distribution of 52% patients were Stage III followed by 31% with high risk Stage II and the remaining 17% were Stage IV in FOLFOX4 arm. In the CAPOX arm a majority 42% were Stage IV followed by 33% with Stage III and 25% were high risk Stage II which is in contrast to the study reported by Yoshihito ohhara *et al* (76) which also included both locoregional and metastatic disease with 49% patients in the FOLFOX4 arm and 42% in CAPOX arm had a locoregional and 51% patients in the FOLFOX4 arm and 58% in CAPOX arm showed a metastatic disease.

Nausea, anemia, peripheral neuropathy and fatigue were similar between the two arms with no statistical significance which is consistent with the Jim Cassidy study *et al.*[4] and a study by Diaz Rubio *et al.*[10] A similar finding was also observed with Michel Ducreus study *et al.*[11]

CAPOX arm is associated with a higher incidence of Grade 2 diarrhea (51.2% v 34.5%) which is in contrast to the study reported by R Baird *et al.*[12] where Grade 2 diarrhea is reported in 8% and Grade 3 in 20% patients. FOLFOX4 arm is associated with a higher incidence of Grade 3 diarrhea (58.6% v 44.2%) which is also inconsistent with the study reported by Andre T *et al.*[13] where Grade 3 diarrhea is observed in 11% patients. The diarrhea reported in the present study with both CAPOX and FOLFOX4 arms is inconsistent with the Jim Cassidy study *et al.*[4] in which CAPOX arm was associated with more Grade 3 diarrhea (19% v 11%) as compared to the FOLFOX4 arm. Another study by Michel Ducreus *et al.*[11] also showed more Grade 3 diarrhea (14% v 7%) with CAPOX arm as compared to the FOLFOX4 arm buta study reported by Diaz-Rubio *et al.*[72] showed a higher incidence of Grade 3 diarrhea (24% v 14%, p<.05) with FOLFOX4 arm as compared to the CAPOX arm. 31% patients in the FOLFOX4 arm reported a Grade 3 vomiting which is in contrast to the Andre T study *et al.*[13] which reported an incidence 5.9%. Similarly, CAPOX is associated with 11.6% Grade 3 vomiting which is also not as reflected with the Michel Ducreux study *et al.*[11] data of reported incidence of 2%. A study by Nikol Snoeren *et al*[14]also reported an incidence of 2.8%. FOLFOX4 arm is associated with a higher incidence of Grade 3 vomiting (31% v 11.6%) as compared to the CAPOX arm is in contrast to the Jim Cassidy study *et al.*[4] data of (4% v 5%) with FOLFOX4 and CAPOX respectively. CAPOX arm is associated with a higher incidence of Grade 1 vomiting (60.5% v 24.1%, p=0.004) as compared to the FOLFOX4 arm which is in contrast with the Jim Cassidy study (68) *et al* where 22% patients in both arms experienced a toxicity of Grade 1 vomiting but it was consistent with the study reported by Dimitrios Pectasides *et al.*[15] which showed vomiting was more frequent in the CAPOX arm (1.57% vs 0%. p=0.012) than FOLFOX arm. Nausea rates were less as compared to the original study of Jim Cassidy *et al.*[4]

Grade 3 peripheral neuropathy reported with the CAPOX arm (12.3%) is similar to the Michel Ducreux study *et al.*[11] in which the Grade 3 peripheral neuropathy is reported in 11% patients. In the FOLFOX4 arm, 15.1% patients experienced the Grade 3 peripheral neuropathy which is as reflected with the Andre T study *et al.*[13] which reported an incidence of 12%. Rates of Grade 3 peripheral neuropathy were similar between the two arms (CAPOX 12.3%, FOLFOX 15.1%) and it was consistent with the Jim Cassidy study *et al.*[4] which reported approximately 17% with both the regimens but it was in contrast to the Michel Ducreus study *et al*[11] where CAPOX arm is associated with less Grade 3 & 4 peripheral neuropathy (11% v 26%) as compared to the FOLFOX arm.

FOLFOX4 arm is associated with a higher incidence of Grade 3 neutropenia (41.4% v 7%, p=.000) and febrile neutropenia (34.5% v 2.3%, p=.000) than CAPOX arm which is consistent with the Jim Cassidy study *et al.*[4] data of Grade 3 neutropenia (44% v 7%) and febrile neutropenia (4.8% v 0.9%) respectively. Another study by Michel Ducreus *et al.*[11] also showed a higher incidence of Grade 3 neutropenia (47% v 5%) and febrile neutropenia (6% v 0%) with FOLFOX4 and CAPOX arms, respectively. Similarly, Yoshihito

ohhara study *et al*.[6] also reflected a higher incidence of Grade 3 neutropenia (55% v 12%) with FOLFOX4 arm as compared to the CAPOX arm. Incidence of Grade 3 neutropenia (41.4%) reported with the FOLFOX4 arm is consistent with the Andre T study *et al*.[13] in which 41% patients reported the similar toxicity with FOLFOX4.

Higher incidence of Grade 1 thrombocytopenia with CAPOX arm as compared to the FOLFOX4 arm (34.9% v 10.3%, *p*=0.035) is inconsistent with the Jim Cassidy study *et al.* data of (4% v 6%) with CAPOX and FOLFOX4 arms, respectively but it was consistent with the study reported by Yu Guo *et al*.[32] The present study showed a similar Grade 3 thrombocytopenia with a rate of 2% with FOLFOX4 arm and 3% with CAPOX arm which is in contrast to the study reported by Michel Ducreus *et al.*[11] where a higher Grade 3 & 4 thrombocytopenia (12% v 5%) is observed with CAPOX arm as compared to the FOLFOX4 arm even though non-significant like the present study.

CAPOX arm is associated with a higher incidence of Grade 2 (51.2% v 0%) and Grade 3 (27.9% v 0%) HFS as compared to the FOLFOX4 arm which is statistically significant (*p*=.000) and consistent with the Rainer Porschen study *et al.*[16] which showed a higher Grade 2/3 HFS in the CAPOX arm (10% v 4%, *p*=0.028) as compared to the FOLFOX4 arm and similar finding was observed with the Jim Cassidy study *et al*.[4] data of Grade 2 (8% v 2%) and Grade 3 (6% v 1%) HFS observed with CAPOX and FOLFOX4 respectively. A study reported by Diaz Rubio E *et al*.[4] also showed a higher incidence of Grade 2 HFS (14% V 5%) with CAPOX arm as compared to the FOLFOX4 arm. Another study by Michel Ducreux *et al*.[11] also reported a higher Grade 3 HFS (3% v <1%) with CAPOX arm as compared to the FOLFOX4 arm.

Fatigue observed in the present study (FOLFOX4 100%, CAPOX 90.7%, *p*=.143) is consistent with the Michel Ducreus study *et al.*[11] which reported an incidence of (FOLFOX 59%, CAPOX 45%) and the Jim Cassidy *et al.*[4] which showed a rate of (FOLFOX4 46%, CAPOX 38%) but is inconsistent with the Dimitrios Pectasides study *et al.* (70%) which reported a rate (FOLFOX 16.2%, CAPOX 19.4%) even though non-significant as other studies.

Incidence of DLTs in patients treated with CAPOX (41, 95.3%) and FOLFOX4 (28, 96.6%) arms were similar. CAPOX is associated with a higher incidence of diarrhea (37.2% v 13.8%, *p*=0.035) and hand-foot syndrome (37.2% v 0%, *p*=0.000) which is consistent with the diarrhea (25.3% v 3.2%, *p*=0.0001) and HFS (21.7% V 1.1%, *p*=0.0001) reported by the Jonathan M. Loreestudy *et al*.,[18] whereas neutropenia (51.7% v 2.3%, *p*=0.000) is higher with the FOLFOX4 arm which is not as reflected with the study by Loree *et al*. Peripheral neuropathy is not different between the two arms is consistent with the Loree *et al.* study.

Compliance between the two groups showed a (CAPOX 60.5%, FOLFOX4 31%) statistical significance (*p*=0.014). With respect to compliance, a limited data from small retrospective and prospective studies on capecitabine rather than CAPOX/FOLFOX 4 exists. A study by Bhattacharya D *et al*.[17] examining the capecitabine use in breast or colon cancer patients in the United Kingdom demonstrated that 23.3% of the 43 patients enrolled in the study had noncompliance. Another UK study by Winterhalder R *et al*.[19] of 177 breast or gastrointestinal cancer patients demonstrated that 9% of patients had some form of noncompliance during their treatment. Simons S *et al*[20], Thivat E *et al*.[21] also showed a similar patient adherence with capecitabine.

An average delay in between the cycles in CAPOX arm of 4.84 days and in FOLFOX4 arm of 8 days demonstrated a difference in compliance between the two arms which was statistically significant (*p*=.001).The difference observed in the dose intake and the number of days the drug consumed as against the planned dose and number of days of capecitabine in the CAPOX arm is attributed predominantly to diarrhoea, fatigue, elderly age, difficulty in swallowing more number of large size tablets/day.

In FOLFOX4 arm a higher incidence of Grade 3 adverse events (diarrhea, neutropenia, fatigue) and febrile neutropenia caused more delays in between the cycles leading to poor compliance. Also since the FOLFOX-4 regimen involves two 22-hour infusions of 5FU at every 14 day intervals resulting in frequent early visits compared to CAPOX arm, a poor compliance and delay in cycles was noticed.

Conclusion

FOLFOX4 arm is associated with a higher incidence of Grade 3 & 4 neutropeniaand febrile neutropenia. CAPOX arm isassociated with a higher incidence of Grade 2 & 3 hand foot syndrome (HFS), grade1 thrombocytopenia andgrade1 vomiting. The overall Grade 3 and 4 toxicity is significant with FOLFOX4 arm as compared to CAPOX arm. Patients who received CAPOX showed a better compliance to

treatment as compared to patients who received FOLFOX4.

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