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Original Research Article

Comparison of the efficacy and safety of the XELOX regimen versus the FOLFOX-4 regimen in metastatic colorectal carcinoma

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ABSTRACT

Background: Colorectal cancer is a major cause of cancer-related mortality worldwide. Common regimens such as FOLFOX-4 and XELOX are widely used in metastatic colorectal carcinoma (mCRC), differing in toxicity profiles and administration methods.
Methods: This quasi-experimental study included 60 patients with histologically confirmed unresectable mCRC treated at BSMMU from April 2021 to March 2022. Patients were equally assigned to two groups: Arm A received XELOX (oxaliplatin+capecitabine) and Arm B received FOLFOX-4 (oxaliplatin+leucovorin+5-FU). Tumor response and toxicity were assessed using WHO and CTCAE v 5.0 criteria.
Results: The median age was 52 years, with 70% male participants. Baseline characteristics were comparable ($p> 0.05$). At 12 weeks, partial response rates were 46.7% in XELOX and 53.3% in FOLFOX-4, with no significant difference ($p=0.605$). After treatment completion, partial response was 40.0% and 46.7%, respectively, while progressive disease was higher in XELOX (33.3% vs 20.0%; $p=0.668$). Median progression-free survival was similar (7.8 vs 8.2 months; $p=0.65$). Grade 3–4 neutropenia was significantly higher in FOLFOX-4 (40.0% vs 0%, $p=0.003$), with febrile neutropenia observed only in this group. XELOX showed higher rates of diarrhea (40.0%) and hand-foot syndrome (23.3%).
Conclusions: Both regimens demonstrated comparable efficacy. XELOX had more gastrointestinal toxicity, whereas FOLFOX-4 showed higher hematological toxicity. XELOX may be a suitable alternative where outpatient convenience is preferred.

Keywords: XELOX, FOLFOX-4, Colorectal cancer, Chemotherapy

INTRODUCTION

Colorectal cancer (CRC) remains a major global health challenge, with an estimated 1.9 million new cases and 935,000 deaths reported in 2020, according to GLOBOCAN.[1] In Bangladesh, rectal cancer is the 8th most common cancer and also the 6th leading cause of incidence in male and 4th in female, as reported by the National Institute of Cancer Research and Hospital.[2] While early-stage colorectal cancer is typically localized and surgically resectable, approximately 15%-30% of patients present with unresectable metastatic disease at the

time of diagnosis.[3] In such cases, the primary treatment approach involves systemic chemotherapy, which aims to relieve symptoms, improve quality of life, and extend progression-free and overall survival.[4] Among available treatment options, the FOLFOX-4 regimen a combination of oxaliplatin with bolus and infusional 5-fluorouracil (5-FU) and leucovorin administered biweekly has become a standard first-line chemotherapy protocol for metastatic colorectal cancer.[5] This regimen demonstrated superior efficacy over previous 5-FU-based treatments in several pivotal phase III trials.[6]

However, the requirement for central venous access, prolonged hospital stays, and continuous infusions contribute to the treatment burden and can negatively impact patients' quality of life. To address these limitations, oral fluoropyrimidines such as capecitabine have been developed. Capecitabine is a prodrug that is enzymatically converted into 5-FU preferentially at tumor sites, thereby reducing systemic toxicity.

Its oral administration also offers greater convenience and avoids the complications associated with intravenous delivery.[7] The XELOX regimen consisting of oral capecitabine administered for 14 days combined with a single intravenous dose of oxaliplatin every three weeks has emerged as an effective alternative to FOLFOX-4. Multiple randomized studies have demonstrated that XELOX offers comparable efficacy with a more manageable toxicity profile and improved patient compliance.[8,9]

Given the comparable clinical outcomes reported in prior studies and the practical advantages of oral chemotherapy, XELOX presents itself as a promising alternative to the standard FOLFOX-4 regimen.[10] However, direct comparisons in local contexts such as Bangladesh are limited. This study aimed to compare the efficacy and safety of the XELOX regimen with the FOLFOX-4 regimen in patients with unresectable metastatic colorectal carcinoma. This evaluation focuses on treatment response, toxicity profiles, and overall tolerability to help guide optimal treatment selection in clinical practice.

METHODS

Study design and participants

This quasi-experimental study was conducted at the Department of Clinical Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total of 60 patients with histopathologically confirmed, unresectable metastatic colorectal carcinoma (AJCC Stage IV) were enrolled between February 2021 and December 2021 using purposive sampling. The sample size was determined based on feasibility and institutional case flow over the study period. Eligible patients were ≥18 years old, with at least one measurable lesion and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Exclusion criteria included prior chemotherapy or radiotherapy, ECOG ≥3, severe hemorrhage requiring urgent radiotherapy, central nervous system metastases, and significant comorbid illnesses (e.g., cardiovascular disease). Treatment was discontinued upon disease progression, unacceptable toxicity, or patient request.

Ethical approval

Ethical clearance was obtained from the Institutional Review Board of BSMMU (No. BSMMU/2021/1265). Written informed consent was taken from all participants using forms in both Bengali and English. Confidentiality was ensured through coded data collection.

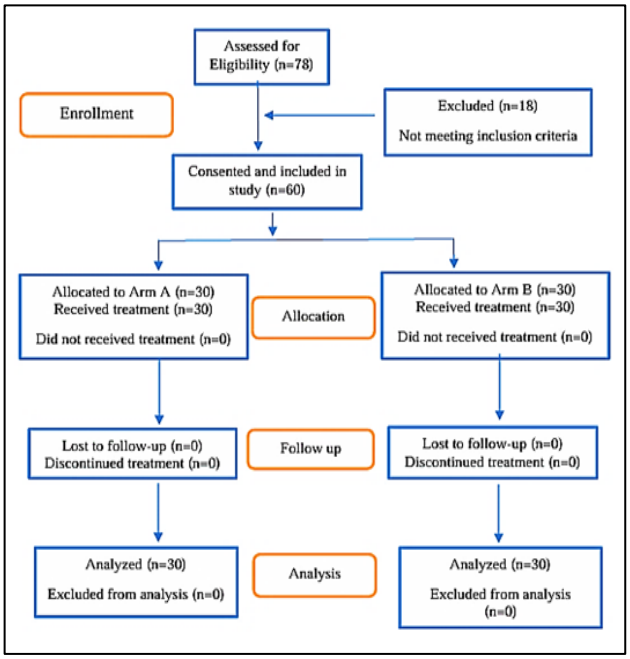

Figure 1: CONSORT flow diagram.

Intervention

Patients were allocated into two groups (Arm A and Arm B) based on their preference and financial capability. Each arm comprised 30 patients.

Arm A (XELOX regimen): Oxaliplatin 130 mg/m² IV on Day 1 and Capecitabine 1000 mg/m² orally twice daily on Days 1–14, repeated every 3 weeks for 8 cycles.

Arm B (FOLFOX-4 regimen): Oxaliplatin 85 mg/m² IV on Day 1, Leucovorin 200 mg/m² IV followed by 5-Fluorouracil 400 mg/m² IV bolus and 600 mg/m² 22-hour infusion on Days 1 and 2, repeated every 2 weeks for 12 cycles.

Premedication and supportive care (e.g., pyridoxine 50 mg twice daily) were provided. Patients were counseled to avoid cold exposure and skin friction to minimize side effects such as hand-foot syndrome.

Assessments

Patients were evaluated before each cycle with physical examination and laboratory tests. Baseline imaging (CT, MRI, or ultrasound) was used to document measurable lesions. Tumor response was assessed mid-treatment (after 4 cycles in Arm A, 6 in Arm B) and post-treatment at weeks 6, 12, and 18, using WHO response criteria. Adverse events were recorded using the NCI CTCAE v 5.0. For analysis, the highest grade of toxicity observed during treatment was considered.

Data analysis

Data were collected using standardized forms, coded, and entered into SPSS version 26. Descriptive statistics were used to summarize baseline characteristics. Between-group comparisons were made using independent t-tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. A two-tailed p-value ≤0.05 was considered statistically significant. All enrolled patients, including those lost to follow-up, were analyzed to minimize attrition bias.

RESULTS

A total of 60 patients were randomized to receive either XELOX (n=30) or FOLFOX (n=30). The median age was 52 years (range, 31–70), with a male predominance of 70%. No significant differences were observed in ECOG performance status, primary tumor sites, or risk factors (all *p*>0.05) (Table 1). In this table, partial response (PR) rates were comparable between XELOX (46.7%) and FOLFOX (53.3%), with stable disease (SD) observed in 30.0% and 33.3% of patients, respectively (*p*=0.605) (Table 2). After the completion of treatment for both arms, PR rates declined slightly in both arms (XELOX: 40.0%; FOLFOX: 46.7%), while progressive disease (PD) increased (XELOX: 33.3%; FOLFOX: 20.0%; p=0.668).

Table 1: Baseline characteristics of study participants (n=60).

Parameter	Arm A (n=30) N (%)	Arm B (n=30) N (%)	P value
Age (years)			
20–30	0 (0.0)	3 (10.0)	0.287
31–40	5 (16.7)	4 (13.3)	
41–50	8 (26.7)	9 (30.0)	
51–60	12 (40.0)	11 (36.7)	
61–70	5 (16.7)	3 (10.0)	
Gender			
Male	20 (66.7)	22 (73.3)	
Female	10 (33.3)	8 (26.7)	
ECOG performance status			
ECOG 0	13.33	10.00	0.852
ECOG 1	46.67	53.33	
ECOG 2	40.00	36.67	
Clinical presentations			
Abdominal pain	12 (40.00)	14 (46.67)	0.602
Altered bowel habit	10 (33.33)	8 (26.67)	0.630
PR bleeding	7 (23.33)	6 (20.00)	0.754
Weight loss	5 (16.67)	2 (6.67)	0.228
Weakness, fatigue	9 (30.00)	7 (23.33)	0.559
Risk factors			
Family history	2 (6.67)	4 (13.33)	0.389
Smoking	19 (63.33)	18 (60.00)	0.791
Red meat intake (>3x/week)	5 (16.67)	3 (10.00)	0.447
Obesity	4 (13.33)	3 (10.0)	0.687
Colorectal polyp	5 (16.67)	7 (23.33)	0.518
Diabetes mellitus	8 (26.67)	6 (20.00)	0.542
Inflammatory bowel disease	1 (3.33)	2 (6.67)	0.554
Primary tumor sites			
Colon	21 (70.00)	17 (56.67)	0.434
Rectum	8 (26.67)	10 (33.33)	
Rectosigmoid junction	1 (3.33)	3 (10.00)	

Table 2: Treatment response observed at the 12-week follow-up (n=60).

Response type	Arm A (n=30) N (%)	Arm B (n=30) N (%)	P value
Complete response	0 (0.0)	0 (0.0)	0.605
Partial response	14 (46.7)	16 (53.3)	
Stable disease	9 (30.0)	10 (33.3)	
Progressive disease	7 (23.3)	4 (13.3)	

Table 3: Treatment responses after the completion of treatment for both arm A and arm B (n=60).

Response type	Arm A (n=30) N (%)	Arm B (n=30) N (%)	P value
Complete response	0 (0.0)	0 (0.0)	0.668
Partial response	12 (40.00)	14 (46.67)	
Stable disease	8 (26.66)	10 (33.33)	
Progressive disease	10 (33.33)	6 (20.00)	

Table 4: Overall acute toxicities in both arms (n=60).

Toxicity	Grade	Arm A (n=30) N (%)	Arm B (n=30) N (%)	P value
Anemia	Grade 1	16 (53.3)	13 (43.3)	0.366
	Grade 2	7 (23.3)	10 (33.3)	
	Grade 3	0 (0.0)	2 (6.7)	
Neutropenia	Grade 1	1 (3.3)	2 (6.7)	0.003
	Grade 2	5 (16.7)	4 (13.3)	
	Grade 3	0 (0.0)	7 (23.3)	
	Grade 4	0 (0.0)	5 (16.7)	
Febrile neutropenia	Grade 3	0 (0.0)	2 (6.7)	0.150
Thrombocytopenia	Grade 1	1 (3.3)	1 (3.3)	0.924
	Grade 2	3 (10.0)	4 (13.3)	
	Grade 3	2 (6.7)	1 (3.3)	
Nausea	Grade 1	10 (33.3)	12 (40.0)	0.827
	Grade 2	7 (23.3)	5 (16.7)	
	Grade 3	2 (6.7)	1 (3.3)	
Diarrhea	Grade 1	8 (26.7)	9 (30.0)	0.326
	Grade 2	6 (20.0)	4 (13.3)	
	Grade 3	6 (20.)	2 (6.7)	
Vomiting	Grade 1	7 (23.3)	6 (20.0)	0.960
	Grade 2	5 (16.7)	4 (13.3)	
	Grade 3	1 (3.3)	1 (3.3)	
Stomatitis	Grade 1	4 (13.3)	7 (23.3)	0.458
	Grade 2	2 (6.7)	3 (10.0)	
	Grade 3	0 (0.0)	1 (3.3)	
Hand-foot syndrome	Grade 1	4 (13.3)	2 (6.7)	0.081
	Grade 2	5 (16.7)	1 (3.3)	
	Grade 3	2 (6.7)	0 (0.0)	
Peripheral neuropathy	Grade 1	11 (36.7)	14 (46.7)	0.617
	Grade 2	10 (33.3)	7 (23.3)	
	Grade 3	3 (10.0)	5 (16.7)	

No complete responses were observed (Table 3). Grade 3–4 neutropenia was significantly higher in Arm B (40.0%) compared to Arm A (0.0%) (p=0.003). Febrile neutropenia occurred only in Arm B (6.7%).

Other toxicities, including anemia, thrombocytopenia, nausea, vomiting, diarrhea, stomatitis, hand-foot syndrome, and peripheral neuropathy, were comparable between the two arms, with no statistically significant differences (Table 4).

Median PFS was 7.8 months with XELOX and 8.2 months with FOLFOX (log-rank p=0.65), with 6-month PFS rates of 58% vs. 62%, respectively (Figure 1).

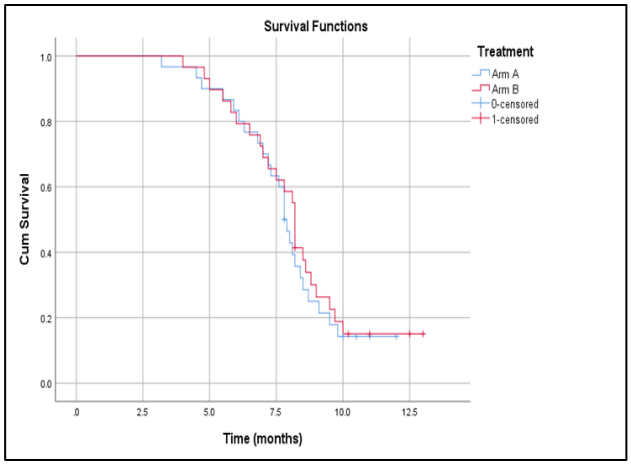

Figure 1: Kaplan-Meier curves comparing progression-free survival between XELOX (median 7.8 months) and FOLFOX (median 8.2 months) treatment arms.

DISCUSSION

CRC remains a major public health concern globally, with a rising incidence and mortality rate in underdeveloped nations (Ferlay et al This study compared the efficacy and safety profiles of XELOX and FOLFOX-4 regimens in metastatic colorectal cancer (mCRC) patients.[11] The mean age of patients in both arms was similar (51.17±9.71 years in Arm A vs. 51.17±11.96 years in Arm B), with a median age of 51.39 years and an age range from 23 to 70 years. The highest incidence was observed in the 51–60 years age group, consistent with Raza et al.[12] Several risk factors were identified among the study population, including smoking (61.67%), diabetes mellitus (23.33%), colorectal polyp (20.00%), high red meat intake (13.33%), family history of CRC (10.00%), and inflammatory bowel disease (5.00%), supporting findings from Sato et al. (2023).[13] Most patients had an ECOG performance status of 1 (46.67% in Arm A and 53.33% in Arm B), while a notable proportion (38.33%) had ECOG 2 –higher than commonly reported in Western populations.

This could be attributed to delayed presentation due to lack of awareness and socioeconomic constraints. The primary endpoint of the study was treatment response. Serial follow-ups at 12, and 18 weeks revealed no complete responses in either arm. Partial response rates remained higher in Arm B throughout, but differences were not significant. At 18 weeks, the overall response rate (ORR) was 40.00% in Arm A and 46.67% in Arm B, again without a significant difference (p=0.668). These findings align with previous studies, such as Ducreux et al reporting an ORR of 42% with XELOX, and Cassidy et al reporting an ORR of 47% with XELOX and 48% with FOLFOX-4.[6,14] Regarding hematological toxicities, anemia rates were comparable between arms, though higher-grade anemia (grade ≥2) was more frequent in Arm B (40.00% vs. 23.33%). Neutropenia was significantly more prevalent in Arm B, affecting 60.00% of patients compared to 20.00% in Arm A (p=0.003). Notably, 40.00% of Arm B patients developed grade 3/4 neutropenia, while no such cases were seen in Arm A. These findings are supported by Guo et al, who reported higher neutropenia rates in the FOLFOX group.[15] Management included infection prevention, antibiotics, and granulocyte colony-stimulating factor where necessary. Thrombocytopenia incidence was similar between groups, with grade 3 thrombocytopenia slightly more common in Arm A (6.67% vs. 3.33% in Arm B), though differences were not significant, aligning with Cassidy et al.[6]

Among non-hematological toxicities, higher-grade (≥2) nausea, vomiting, and diarrhea were more frequent in Arm A, which can be attributed to capecitabine in the XELOX regimen. For instance, grade 2 or higher diarrhea occurred in 40.00% of Arm A versus 20.00% in Arm B (p=0.326), consistent with Rothenberg et al.[8] Hand-foot syndrome, a known capecitabine toxicity, was notably more frequent in Arm A (36.67% vs. 10.00% in Arm B), aligning with findings by Rothenberg et al and Ducreux et al.[8,14] Stomatitis was observed more in Arm B, with grade 3 stomatitis reported in 3.33% of patients compared to none in Arm A.

This is consistent with Cassidy et al and Zhang et al, who reported higher stomatitis rates with 5-FU-based regimens.[6,16] Peripheral neuropathy, a common oxaliplatin toxicity, was reported in 80.00% of Arm A and 86.67% of Arm B patients. Grade 3 neuropathy was more common in Arm B (16.67% vs. 10.00% in Arm A), likely due to the higher cumulative oxaliplatin dose in the FOLFOX-4 regimen.

Progression-free survival was also comparable between the two groups. median PFS was 7.8 months with XELOX and 8.2 months with FOLFOX, with similar 6-month PFS rates (58% vs. 62%). These results align with Park et al (7.5 months with oxaliplatin-capecitabine) and exceed those of Kim, and Salah-Eldin, who reported median PFS ranging from 5.6 to 6 months.[17-19] Overall, both regimens in our study showed comparable efficacy.

Limitations

The duration of the study was limited to one year, which may not have been sufficient to capture long-term treatment outcomes or late-onset toxicities.

CONCLUSION

This study demonstrates that both the XELOX and FOLFOX-4 regimens are similarly effective in managing metastatic colorectal carcinoma. While XELOX is associated with a higher incidence of gastrointestinal toxicity, FOLFOX-4 leads to more severe hematological adverse events, particularly neutropenia. Given its oral administration and reduced need for hospital visits, XELOX may be a preferable option in resource-constrained or outpatient-centered settings.

Recommendations

Further multicenter, randomized controlled trials with larger cohorts are recommended to validate these findings and explore the impact of regimen choice on quality of life, cost, and long-term survival outcomes in diverse patient populations.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee (No. BSMMU/2021/1265)

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