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ORIGINAL ARTICLE

Efficacy and Safety of Xelox in Comparison with Folfox in Metastatic Colorectal Cancer

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ABSTRACT

Background: The study aimed to evaluate efficacy and safety of Xelox in comparison to Folfox chemotherapy for metastatic colorectal cancer.

Methods: A quasi experimental study was undertaken at the Department of Oncology, Jinnah Postgraduate Medical Center between April 2022 to November 2022. All the patients coming to oncology department JPMC with confirmed diagnosis of metastatic colorectal cancer of age 18 years and above were included. All data were recorded in a predefined proforma by the researchers. Patients' age, gender, and comorbidity, family history, and clinical characteristics were noted. The primary endpoints were the overall response rates and the frequency of adverse effects.

Results: A total of 200 patients were enrolled with a mean age of 40 ± 14.38 years. There were 100 participants in the Xelox group while 100 participants in the Folfox group. About 45 (45%) in the Xelox group and 62 (62%) in the Folfox group reported adverse effects of the chemotherapy (p=0.015). The rate of neutropenia grade III/IV was greater in the Folfox category than the Xelox. Hand foot syndrome was significantly more frequently reported in the Xelox group than the Folfox group 22 (48.89%) and 18 (29.03%); p=0.036, respectively. Oral mucositis was also more frequently reported in patients taking Xelox than Folfox [20 (44.44%) vs. 15 (24.19%); p=0.023]. There was no significant statistical difference between Xelox and Folfox in terms of patient overall response rates.

Conclusion: According to the study, there are no appreciable differences between Xelox and Folfox chemotherapy in terms of overall response rates among patients with colorectal cancer. However, overall, patients taking Folfox reported significantly higher rates of adverse effects with the exception of hand foot syndrome and oral mucositis which was more frequent in the Xelox group.

Keywords: colorectal carcinoma, chemotherapy, xelox, folfox, Capecitabine, Oxaliplatin, fluorouracil

INTRODUCTION

With 600,000 fatalities and 1.2 million new cases per year worldwide, colorectal cancer is the second most common killer.[1] The metastatic colorectal cancer is associated with a very low survival rate of 10% or even lower. [2]

Generally, a holistic approach for the management and treatment is prioritized by oncologists in colorectal cancer patients, and chemotherapy is one of the most important management techniques. Chemotherapy that is safe and effective can extend patients' lives and enhance their quality of life. [3] The chemotherapy for colorectal cancer has frequently used 5-FU. Capecitabine (CAP), an oral fluorouracil precursor medication, was shown in a number of worldwide studies to be a safe and effective treatment for colorectal cancer in 2001.[4-5]

Xelox is the amalgamated form of Capecitabine and Oxaliplatin while Folfox is fluorouracil and Oxaliplatin. Oxaliplatin is the platinum analogue while capecitabine and fluorouracil are antimetabolites.[6-7]

In a study by Ducreux et al Xelox versus Folfox-6 was compared as the treatment of metastatic colorectal cancer.[7] The total response rate in the population with the intention to treat was approximately 40% in the Xelox category while forty six percent in the Folfox category. The variability between the groups was 6.9%, and the unilateral 95% confidence interval's top limit of 16.2% was higher than the non-inferiority margin of 15%. In comparison to folox, xelox was linked to a tendency for higher hand foot syndrome (p = 0.088).[7]

There have been some trials from the Western world as well, however, none from Pakistan. There is a considerable gap related to the efficacy of Xelox versus Folfox in the local population. Therefore, to cover up the literature gap in our population, the study was undertaken. The objective of the current study was to assess the efficacy and safety of Folfox in comparison with Xelox in individuals with Metastatic Colorectal Cancer

METHODOLOGY

A quasi experimental study was conducted at the Department of Oncology, Jinnah Postgraduate Medical Center between April 2022 to November 2022. Before the data acquisition, the researchers acquired ethical approval from the institutional review board of JPMC with a reference number of F2-81/2022-GENL/180/JPMC.

All the patients who presented to the oncology department, JPMC with confirmed diagnosis of denovo metastatic colorectal cancer, aged 18 years or older were eligible to partake in the study. However, those with localized or recurrent colorectal cancer, pregnant or breast-feeding women, those with renal failure, hepatic failure or those who did not give consent of participation were excluded from the study.

A non-probability consecutive sampling technique was utilized to select participants in each group. The sample size calculation was done using WHO sample size calculator using the reference response rates of 39% and 46% with Xelox and Folfox, respectively in the "intention to treat" (ITT) group.[7] By keeping the confidence level of 95%, a sample size of 96 (in each group) was determined.

Patients were narrated the risks and side effects of both the drugs before including them in the study. Only patients who provided full verbal and written consent to participate were included. All data were recorded in a predefined proforma by the researchers. The recorded data included the age of the patient, gender, comorbidity, family history, and clinical characteristics, tumor assessments via CT scans and MRI, adverse effects, and toxicity.

The primary endpoint was the overall response rate and secondary outcome was the safety profile of the drug. Overall response rate was assessed by Chest, Abdomen and Pelvis CT with contrast for each group via assessing the tumor response after 4-6 cycles of chemotherapy, and ii) secondary endpoint was the adverse effects of the drug.

All continuous variables (age, weight, height, BMI, tumor size, etc) were presented as mean and standard deviation while, all categorical values (gender, side effects, tumor response rate) were presented in proportions. Chi square tests were applied to assess the differences between rates of adverse effects in each group. If the cell value was < 5 then, Fisher exact test was utilized. A p-value of less than 0.05 was deemed as the cut off for statistical significance.

During data collection, only principal investigators had access to patient data - no personal identifiers like name of the patient or address were recorded. Anonymity and confidentiality were maintained throughout the study. Pseudo Names were used and coded before data collection to maintain confidentiality of all patients.

RESULTS

A total of 124 patients were enrolled with a mean age of 40 ± 14.38 years. The majority were males. The mean duration of disease was 9.15 ± 9.28 months. The ratio of Xelox and Folfox was 1:1 with 100 participants in each group. A mean number of cycles of chemotherapy was 5.3 ± 1.65 with a mean duration of treatment of 5 ± 2.24 months as illustrated in Table 1. Table 2 reveals the biochemical profile of the patients.

Table 1: Sociodemographic and clinical characteristics of the Study Participants

Parameters	Xelox (n=100)	Folfox (n=100)	p-value
Age (years)	40.01 ± 14.4	39.97 ± 14.4	0.989
Gender			
Female	37 (37.00%)	38 (38.00%)	0.515
Male	63 (63.00%)	62 (62.00%)	
Comorbidity			
Diabetes Mellitus Type II	37 (67.27%)	32 (64.00%)	
Hypertension	18 (32.73%)	18 (36.00%)	
Family history of malignancy	3 (3.00%)	2 (2.00%)	
Mean Drug cycles	5.40 ± 1.71	4.92 ± 1.58	0.141
Mean Dose duration (months)	5.14 ± 2.24	3.0 ± 1.11	0.374
Grade			
Grade 1	4 (4.00%)	0	0.230
Grade 2	72 (72.00%)	70 (70.00%)	
Grade 3	24 (24.00%)	30 (30.00%)	

We did not find any significant statistical difference between Xelox and Folfox with regards to patient response rates as illustrated in Table 3. 12 patients in the Xelox group and 13 patients in the Folfox group showed complete response; however, the variance was not significant (p=0.960).

Table 2: Patient Outcomes and Overall Response Rate in Xelox versus Folfox

Overall response rate	Xelox	Folfox	p-value
Partial Response	45 (45.00%)	42 (42.00%)	0.960
Complete Response	12 (12.00%)	13 (13.00%)	
Progressive Disease	13 (13.00%)	15 (15.00%)	
Stable Disease	30 (30.00%)	31 (31.00%)	

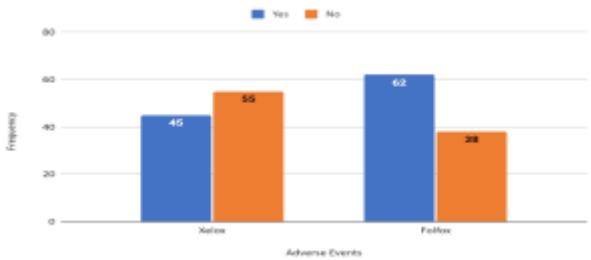

Figure 1: Comparison of adverse events in Xelox (n=100) vs. Folfox (n=100); (p=0.015)

About 45 (45%) in the Xelox group and 62 (62%) in the Folfox group reported adverse effects of the chemotherapy (p=0.015) (Figure 1).

Discontinuation of chemotherapy due to undesired effects occurred in 17 patients in the Xelox group and 21 patients in the Folfox group (p=0.676). The rate of neutropenia grade III/IV was slightly higher in the Folfox group than the Xelox. Hand foot syndrome was significantly more frequently reported in the Xelox group than the Folfox group 22 (48.89%) and 18 (29.03%); p=0.036, respectively. Oral mucositis was also more frequently reported in patients taking Xelox than Folfox [20 (44.44%) vs. 15 (24.19%); p=0.023] (Table 3).

Table 3: Distribution of Adverse Events in Xelox (n=45) versus Folfox (n=62)

Parameters	Xelox (n=45)	Folfox (n=62)	p-value
Did adverse event require discontinuation of therapy			
Yes	17 (37.7%)	21 (33.8%)	0.676
No	28 (62.2%)	41 (66.1%)	
Neutropenia (Grade III/IV)	10 (22.22%)	18 (29.03%)	0.428
Granulocytopenia	13 (28.89%)	15 (24.19%)	0.585
Neurosensory toxicity	11 (24.44%)	14 (22.58%)	0.822
Anemia	10 (22.22%)	20 (32.26%)	0.253
Diarrhea	15 (33.33%)	15 (24.19%)	0.275
Vomiting	15 (33.33%)	17 (27.42%)	0.509
Hand foot syndrome	22 (48.89%)	18 (29.03%)	0.036
Nausea	19 (42.22%)	26 (41.94%)	0.976
Oral mucositis	20 (44.44%)	15 (24.19%)	0.023
Thrombocytopenia	8 (17.78%)	12 (19.35%)	0.836
Renal insufficiency	9 (20.00%)	8 (12.90%)	0.321

DISCUSSION

The present study explored the overall response rate and safety profile of chemotherapy with Xelox versus Folfox for metastatic colorectal cancer. The study revealed that the Folfox and Xelox chemotherapy do not have significant differences with regards to the overall response rates among individuals with metastatic colorectal cancer. However, hand foot syndrome and oral mucositis were both considerably more commonly reported in the Xelox group than the Folfox group.

Yu Guo et al., conducted a meta-analysis using Xelox and Folfox, which included data from a total of 4363 patients.[8] Eight of the investigations provided information on adverse events of at least grade 3. Results from a pooled analysis showed that the Xelox group experienced a higher incidence of low platelet count ($p = 0.0005$), hand foot syndrome ($p < 0.00001$), and diarrhea ($p < .00001$) than the Folfox group. There were no statistically difference changes in the frequency of adverse effects in grades 3/4, including anemia and gastrointestinal issues.

To prove that Xelox is not better or worse than Folfox as first-line therapy for patients with metastatic colorectal cancer, Ducreux M et al., began a randomized trial in 2006. For six months, 306 individuals were assigned to receive either Xelox or Folfox. The response rate was 42% with Xelox and 46% with Folfox. Frequency of hand-foot syndrome, low platelet count, and diarrhea among Xelox patients was higher, but fewer cases of febrile neutropenia and neuropathy were observed. The percentage of patients who stopped taking their medication due to adverse effects was 19% in the Xelox arm and 23% in the Folox arm. Compared to Folfox-6, Xelox showed no inferiority and had an excellent safety profile in first-line metastatic colorectal cancer.[9]

According to the research by Cassidy et al Xelox was linked to more cases of grade 3 diarrhea and grade 3 hand-foot syndrome. In contrast, Folfox was linked to more cases of grade ¾ neutropenia/granulocytopenia and febrile neutropenia. In cancer patients, overall survival rate is the most relevant and objective indicator of effectiveness. However, when this objective is used,

second-line and later-lines of chemotherapy may obscure any differences across study treatments.[11]

Masato K and coworkers have investigated the benefits of combining first step chemotherapy and monoclonal antibodies for the management of patients with colorectal cancer with liver metastasis.[12] Patients with metastasized colorectal cancer were studied to determine if an Folfox or Xelox combined with monoclonal antibiotics (cetuximab or bevacizumab) improved survival rate. Twenty-one (45%) patients had adverse events of Grades 3/4 and 55 of the patients/subjects reacted favorably to treatment. Patients with wild-type KRAS had much smaller tumors than those with mutant KRAS. The median progression -free survival survival (PFS) was 15.6 months, with a resection rate of 83% and a postoperative morbidity rate of 14%. [12]

Another meta-analysis examined Folfox and Xelox treatment in individuals with metastatic colorectal cancer, but this time only looked at Randomized Controlled Trial (RCT) studies. Neither Folox nor Xelox showed any statistically significant advantages regarding the overall response rate. Toxicities of level 3 and 4 were reported across all investigations. The combined study showed that the proportion of thrombocytopenia, Hand Foot Syndrome (HFS), and diarrhea was more significant in the Xelox Group.[13] The buof hand foot syndrome was also significantly higher in our study.

In contrast to our findings, Yu Gou et al., found that Xelox group members were more likely to experience neutropenia, diarrhea, and thrombocytopenia than Folfox group members.[8] Nevertheless, it was claimed that the effect of XELOX is similar to FOLFOX in patients with metastatic colorectal cancer.[14-18]

While the overall response rates of both the therapies were similar, Xelox monotherapy had two vivid advantages over Folfox therapy. Firstly, an oral mode of administration alleviates the need for a hospital admission which makes Xelox a more feasible option for patients who have an embedded fear of hospitals as well as reduced financial burden. It also made Xelox a more practical option in the COVID-19 pandemic situation for the last few years. Secondly, Xelox has a relatively lower incidence of adverse effects. This allows for good compliance and a better quality of life in our patients.

One major limitation of the present study is that there was no data collected on patient compliance. Secondly, a small sample size limited interference from the findings. Therefore, further multi-center studies should be conducted to ascertain the findings of the current study.

CONCLUSION

The study found no discernible differences in overall response rates between patients with colorectal cancer treated with Xelox and Folfox treatment. With the exception of hand-foot syndrome and oral mucositis, which were more frequent in the Xelox group, patients using Folfox reported overall considerably greater rates of adverse events.

REFERENCES

1. Jemal A, Murray T, Ward E, Samuels A. Cancer statistics, 2005 (vol 55, pg 10, 2005). Ca-a Cancer Journal for Clinicians. 2005 Jul 1;55(4):259-.
2. Fernández Montes A, López López C, Argilés Martínez G, Páez López D, López Muñoz AM, García Paredes B, et al. Prognostic nomogram and patterns of use of FOLFIRI-Aflibercept in advanced colorectal cancer: a real-world data analysis. The Oncologist. 2019 Aug;24(8):e687-95.
3. Park YH, Lee JL, Ryoo BY, Ryu MH, Yang SH, Kim BS, Shin DB, Chang HM, Kim TW, Yuh YJ, Kang YK. Capecitabine in combination with Oxaliplatin (XELOX) as a first-line therapy for advanced gastric cancer. Cancer chemotherapy and pharmacology. 2008 Apr;61(4):623-9.
4. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-1ine treatment in 605 patients with metastatic colorectal cancer-results of a randomized phase III study. J Clin Oncol 2001;19:282– 2292.
5. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patient with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 2001;19:4097–4l06
6. Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, Debraud F, Figer A, Grossmann J, Sawada N, Schoffski P. XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. Journal of Clinical Oncology. 2004 Apr 13;22(11):2084-91.
7. Ducreux M, Bennouna J, Hebbar M, Ychou M, Lledo G, Conroy T, Adenis A, Faroux R, Rebischung C, Bergougnoux L, Kockler L. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. International journal of cancer. 2011 Feb 1;128(3):682-90.
8. Guo Y, Xiong BH, Zhang T, Cheng Y, Ma L. XELOX vs. FOLFOX in metastatic colorectal cancer: An updated meta-analysis. Cancer investigation. 2016 Feb 7;34(2):94-104.
9. Ducreux M, Bennouna J, Hebbar M, Ychou M, Lledo G, Conroy T, Adenis A, Faroux R, Rebischung C, Douillard J. Efficacy and safety findings from a randomized phase III study of capecitabine (X)+ oxaliplatin (O)(XELOX) vs. infusional 5-FU/LV+ O (FOLFOX-6) for metastatic colorectal cancer (MCRC). Journal of Clinical Oncology. 2007 Jun 20;25(18_suppl):4029-.
10. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Rittweger K, Gilberg F, Saltz L. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer. 2011 Jun 28;105(1):58-64. doi: 10.1038/bjc.2011.201. Epub 2011 Jun 14. PMID: 21673685; PMCID: PMC3137415.
11. Di Leo A, Buyse M, Bleiberg H (2004) Is overall survival a realistic primary end point in advanced colorectal cancer studies? A critical assessment based on four clinical trials comparing fluorouracil plus leucovorin with the same treatment combined either with oxaliplatin or with CPT-11. Ann Oncol 15: 545–549
12. Kataoka, M., Kanda, M., Ishigure, K. et al. The COMET Open-label Phase II Study of Neoadjuvant FOLFOX or XELOX Treatment Combined with Molecular Targeting Monoclonal Antibodies in Patients with Resectable Liver Metastasis of Colorectal Cancer. Ann Surg Oncol 24, 546–553 (2017). https://doi.org/10.1245/s10434-016-5557-9
13. Budhi IB. 111P A meta-analysis study on safety and effectiveness comparison between FOLFOX and XELOX regiments on advanced stage colorectal cancer. Annals of Oncology. 2020 Nov 1;31:S1284.
14. Sánchez-Gundín J, Fernández-Carballido AM, Martínez-Valdivieso L, Barreda-Hernández D, Torres-Suárez AI. New trends in the therapeutic approach to metastatic colorectal cancer. International journal of medical sciences. 2018 Apr 3;15(7):659-65.
15. Maiello E, Di Maggio G, Cordio S, Cinieri S, Giuliani F, Pisconti S, Rinaldi A, Febbraro A, Latiano TP, Aieta M, Rossi A. Bevacizumab in combination with either FOLFOX-4 or XELOX-2 in first-line treatment of patients with metastatic colorectal cancer: a multicenter randomized phase II Trial of the Gruppo Oncologico dell'Italia Meridionale (GOIM 2802). Clinical Colorectal Cancer. 2020 Jun 1;19(2):109-15.
16. Belgasem F, Aboshala A, Elbaruni S. The Influence of Capox (Xelox) and Folfox on Colorectal Cancer Patients in Tripoli University Hospital, Tripoli, Libya. Libyan International Journal of Oncology. 2022 Jun 26:28-31.
17. Baraniskin A, Buchberger B, Pox C, Graeven U, Holch JW, Schmiegel W, Heinemann V. Efficacy of bevacizumab in first-line treatment of metastatic colorectal cancer: a systematic review and meta-analysis. European Journal of Cancer. 2019 Jan 1;106:37-44.
18. Giuliani J, Bonetti A. First-line therapies in metastatic colorectal cancer: integrating clinical benefit with the costs of drugs. International Journal of Colorectal Disease. 2018 Nov;33(11):1505-16.