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Original Article

Randomized Trial of FOLFOX 4 and FOLFIRI in The Treatment of Advance Colorectal Cancer

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ABSTRACT

Colorectal cancer is a major global health concern, ranking third in prevalence and second in mortality. Developed countries have high incidence rates, while Pakistan is considered a low-risk region. Metastatic colorectal cancer requires targeted therapies like FOLFIRI and FOLFOX 4, but their effectiveness in Pakistan is unknown. This study aims to provide insights, guide treatment decisions, and expand global understanding in the field. **Objective:** To compare therapeutic effects of FOLFOX 4 and FOLFIRI for advanced colorectal cancer patients. **Methods:** The Medical Oncology Department of Jinnah Postgraduate and Medical Centre conducted a randomized controlled trial research from May 2022 to February 2023. Hundred patients of advanced colorectal cancer with a confirmed diagnosis of age 18 to 80 years, of either gender, were included. Randomly, 50 of these patients were in FOLFIRI group, and 50 in FOLFOX4 group. Both groups were compared for the treatment outcomes. **Results:** In the FOLFIRI group, the total response rate was 66%, whereas in the FOLFOX 4 group, it was 78%. In the FOLFIRI group, the median time to progression was 8 months, but in the FOLFOX 4 group, it was 9 months (p=0.06). In the FOLFIRI group, the total median survival time was 13 months, whereas in the FOLFOX 4 group, it was 14 months (p=0.280). **Conclusions**: The response rates between the two groups were similar, while FOLFOX 4 had a little higher rate of tumor control. FOLFIRI had a lower incidence of neutropenia, whereas FOLFOX 4 had a lower incidence of nausea and vomiting.

INTRODUCTION

Colorectal cancer ranks as the third most prevalent cancer and the second leading cause of death worldwide. In 2020, globally, there were over 1.9 million new colorectal cases, resulting in more than 930,000 deaths [1]. Developed countries like Europe, New Zealand, Australia, and North America have a high incidence rate of colorectal cancer [2]. However, countries in Southern Asia have the lowest incidence rates and Pakistan is regarded as a low-risk region for colorectal cancer [2, 3]. Nearly one in five colorectal cancer patients already had distant metastases at the time of diagnosis. Targeted therapies and systemic chemotherapy are advised treatments for metastatic colorectal cancer (mCRC) [4]. In the past, folinic acid (CF) and fluorouracil (5-FU) were the primary first-line therapies for mCRC. However, in the twenty-first century, chemotherapy regimens such as FOLFIRI (CF, 5-FU, and irinotecan) and FOLFOX 4 (CF, 5-FU, and oxaliplatin) have shown success as 1st line treatments for advanced stage colon cancer, improving the prognosis and quality of life for patients [5-10]. A phase III study conducted by Colucci et al., compared the effectiveness of FOLFIRI and FOLFOX4 regimens for treating advanced colorectal cancer. The FOLFIRI regimen was linked to a greater death rate during the first 60 days of treatment, despite the fact that both

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regimens had comparable overall response rates (31% for FOLFIRI and 34% for FOLFOX4) [11]. Another recent study by Neuget et al., found no discernible difference between FOLFOX 4 and FOLFIRI in terms of survival, however FOLFIRI demonstrated a progression-free survival of 7 months and an overall response rate of 39% [12].

These studies highlight the value of individualized treatment programme for individuals with advanced colorectal cancer and the continued pursuit of the most effective therapeutic approaches. Although both regimens have shown benefits for patients with advanced colorectal cancer, there is limited data on their use in Pakistan. This trial aims to provide valuable insights into the effectiveness of these treatments specifically in the Pakistani population and identify any differences in response and side effects. The results of this study will guide clinical decision-making, contribute to the development of standardized treatment guidelines for advanced colorectal cancer patients in Pakistan, and expand the global understanding of optimal treatment strategies. Furthermore, it may pave the way for further research in this field.

METHODS

It was an interventional study carried out at the department of Medical Oncology, Jinnah Postgraduate and Medical Center from May 2022 to Feb 2023. Sample size of 92≈100 (50 in each group) was estimated using Open epi sample size calculator by taking statistics of overall response rate of FOLFIRI as 39%, margin of error as 10% and 95% confidence level. The included patients of age 18 to 65 years of both sex with confirmed diagnosis of advanced colorectal carcinoma (stage III-IV). Patients with history of uncontrolled and active infections, previous chemotherapy including irinotecan or oxaliplatin, carcinomatous meningitis or known brain metastases, interstitial fibrosis or interstitial pneumonia, total colectomy, history of any cardiovascular event, lactating or pregnant females, and psychological or mental disorders were excluded from the study. Non-random consecutive sampling method was employed. All eligible patients provided informed consent, and the study taken approval from the ethical review committee. Subjects were divided into two groups using a 1:1 random ratio. Group A, consisting of 50 individuals, was administered the FOLFIRI regimen. This particular regimen involves administering leucovorin 100 mg/m2 (L-isomer form) as a two-hour infusion, followed by a bolus injection of 5-fluorouracil 400 mg/m2. On the initial day, patients in this group were additionally administered irinotecan 180 mg/m2 (150 mg/m2 for those aged over 70-75 years). Furthermore, leucovorin 100 mg/m2 (L-isomer form) was given as a two-hour infusion before a bolus injection of 5-fluorouracil 400 mg/m2, followed by a 22-hour infusion of 5-fluorouracil 600 mg/m2. Group B, also comprising of 50 individuals, received solely the FOLFOX4 regimen. This regimen includes oxaliplatin 85 mg/m2 on the first day, along with leucovorin and 5-fluorouracil on both days 1 and 2. Both treatments were administered at two-week intervals for a maximum of 12 cycles. The response rate of each patient was assessed, with complete response and partial response used as criteria. CT scans were conducted before and after the therapy at follow-up visits every eighth week to evaluate the response. The toxicity of each treatment cycle was also evaluated. The data analysis were performed using SPSS version 23.0. The median and interquartile range were used to report the age, time to progression, and survival time. Frequency and proportions were reported for gender, ECOG status, prior therapy, primary tumor site, site of metastasis, response, and toxicity. To conduct a comparative analysis of the response to treatment of the two groups, the Fisher's exact test was employed. Furthermore, the Mann-Whitney U test was utilized to compare the median time to progression and overall survival of the two groups. It was conventionally agreed that a p-value of equal to or less than 5% would be indicative of statistical significance.

RESULTS

The mean age was 37.5 years in FOLFIRI group and 44.5 years in FOLFOX 4 group. Most of the patients with advance colorectal cancer were males, had ECOG performance status as 1, previously received adjuvant chemotherapy and primary colon cancer in both groups. While, 42% patients had liver metastases in FOLFIRI group and 36% in FOLFOX 4 group, respectively (Table 1).

Table 1: Patients' characteristics in both groups

Characteristics	FOLFIRI (n=50)	FOLFOX 4 (n=50)
Age (years)	37.5 (28-53)	44.5 (35-50)
Gender		
Female	19 (38)	16 (32)
Male	31 (62)	34 (68)
ECOG performance status		
0	33 (66)	25 (50)
1	13 (26)	18 (36)
2	4 (8)	7 (14)
Prior therapy		
Adjuvant chemotherapy	33 (66)	30 (60)
Primary tumor resection	17 (34)	20 (40)
Primary tumor site		
Colon	32 (64)	33 (66)
Rectum	13 (26)	12 (24)
Colon and rectum	5 (10)	5 (10)
Site of metastasis		
Liver	21 (42)	18 (36)
Lungs	13 (26)	11 (22)

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Lymph nodes	4 (8)	2 (4)
Brain	1 (2)	0
Bone	1 (2)	2 (4)
Peritoneum	2 (4)	4 (8)
Pelvis	0	6 (12)
Multiple sites	8 (16)	7 (14)
Data presented as Median (IQR) or n (%)		

In the FOLFIRI group, complete response was achieved in 30%, whereas, partial response was achieved in 46%. In FOLFOX 4 group, the complete response was achieved in 24% and partial response was achieved in 52%. The p-value for the Fisher Exact test is 0.145, which greater than 0.05. Hence, there is insignificant difference in response between the two groups, FOLFIRI and FOLFOX 4 (Table 2).

Table 2: Comparison of response rates between both groups

Response	FOLFIRI (n=50)	FOLFOX 4 (n=50)	p-value
Complete response	10 (30)	11 (24)	0.145
Partial response	23 (46)	28 (52)	
Stable disease	6 (12)	8 (16)	
Progressive disease	11 (22)	3 (6)	
Data presented as n (%)			

Additionally, the median time to progression in the FOLFIRI group was 8 months, compared to 9 months in the FOLFOX 4 group. The comparison for median time to progression was done using Mann-Whitney U test, which showed statistical insignificant difference between both groups (p=0.06). In the FOLFIRI group, the total median survival time was 13 months, whereas in the FOLFOX 4 group, it was 14 months. The comparison for total median survival time was done using Mann-Whitney U test, which showed statistical insignificant difference between both groups (p=0.280)(Table 3).

Table 3: Comparison of time to progression and time to survival between both groups

Parameter	FOLFIRI (n=50)	FOLFOX 4 (n=50)	p-value
Median Time to Progression (months)	8	9	0.060
Median Time to survival (months)	13	14	0.280
Data presented as median			

Table 4 displays the toxicity profiles of both therapies. The most prevalent side effects in the FOLFIRI group were anemia (44%), neutropenia (46%) and nausea and vomiting (60%) in that order. The most prevalent toxicity in the FOLFOX 4 group was neutropenia (48%), followed by anemia (36%) and diarrhea (30%).

Table 4: Toxicity profile of both groups

Toxicity	FOLFIRI (n=50)	FOLFOX 4 (n=50)
Neutropenia	23 (46)	24 (48)
Anemia	22 (44)	18 (36)
Thrombocytopenia	7 (14)	8 (16)
Leukopenia	9 (18)	7 (14)
Nausea and vomiting	30 (60)	10 (20)
Diarrhea	19 (38)	15 (30)
Fever	11 (22)	10 (20)
Data presented as n (%)		

DISCUSSION

This particular study was designed with the objective of comparing the efficacy and toxicity of two different chemotherapy regimens, namely FOLFIRI and FOLFOX 4, among patients who are suffering from advanced-stage colorectal cancer. Upon observing the baseline characteristics of the study population, it was observed that both treatment groups exhibited similarities with respect to age, gender, performance status, and previous chemotherapy history. Most of the patients had liver metastases and colon cancer. Elzouki et al., conducted a study on 152 CRC patients and found the median age was 57.4 ± 12.92 years, 55% of the patients were males, and 68% had colon cancer [13]. Similarly, one more study by Masi et al., reported the median age was 62 years and 63% of the patients were males (63%) and colon was the most common site (73%). Additionally, 81% patients had liver as the site of metastases and 68% had synchronous metastases. They observed that baseline characteristics were comparable between the FOLFIRI and FOLFOX 4 treatment groups [14]. Our study examined treatment outcomes and found that the FOLFOX 4 group had a higher overall response rate (78%) compared to the FOLFIRI group (66%). However, the FOLFOX 4 group demonstrated significantly better tumor control rates (94%) compared to the FOLFIRI group (78%). Although the median time to progression was slightly longer in the FOLFOX 4 group, this difference was not statistically significant. Likewise, the median overall survival time did not significantly differ between the two groups. However, the FOLFOX 4 group exhibited a higher 1-year survival rate (58%) compared to the FOLFIRI group (50%). Regarding toxicity profiles, the FOLFIRI group experienced a higher incidence of nausea and vomiting, while the FOLFOX 4 group had higher incidences of neutropenia and diarrhea. However, the overall occurrence of adverse events was similar in both groups. Wu et al., conducted a network meta-analysis to evaluate the effectiveness of various first-line chemotherapy regimens for advanced colorectal cancer. The study revealed that FOLFOX 4, FOLFIRI, and TOMOX demonstrated superior short-term and long-term efficacy compared to other regimens. Based on their findings, the authors recommended these three regimens as suitable options for the clinical treatment of advanced colorectal cancer [15]. Another study by Neuget et al. reported that

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both FOLFOX 4 and FOLFIRI exhibited comparable response rates ranging from 54% to 56%, along with similar progression-free survival rates of approximately 8 months to 8.5 months, respectively. However, patients receiving FOLFOX 4 treatment had a higher probability of experiencing neuropathy, while those undergoing FOLFIRI treatment reported a greater incidence of adverse side effects such as nausea, diarrhea, and neutropenia. The study did not observe a significant disparity in survival outcomes between the two treatment approaches [12]. In another RCT by Ikoma et al., found that FOLFOX 4 and FOLFIRI are both effective combination therapies for treating advanced and metastatic colorectal carcinoma. Both FOLFOX 4 and FOLFIRI have shown similar response rates and overall survival rates. FOLFOX 4 has been associated with more neuropathy, while FOLFIRI has been associated with more diarrhea and neutropenia [16]. In a review article by Idress and Tejani regarding elder patients, it was disclosed that both the FOLFOX 4 and FOLFIRI chemotherapy regimens have demonstrated advantageous outcomes in terms of response and survival rates for elderly patients diagnosed with metastatic colon cancer. Nonetheless, it is important to note that these treatments also pose the risk of drug toxicities, which can potentially be more severe in the elderly population. Therefore, when selecting a treatment plan, it is imperative that the decision is made on a case-by-case basis, with consideration of the patient's overall health and the potential risks and benefits associated with the treatment [17]. Stintzing et al., discussed the findings of the FIRE-3 trial, which conducted a comparative analysis of two distinctive treatment regimens for patients with RAS wild-type metastatic colorectal cancer. It was determined that the response rates were similar for both FOLFOX 4 and FOLFIRI when combined with either cetuximab or bevacizumab. Furthermore, it was observed that the overall survival was comparatively longer for patients who received FOLFIRI plus cetuximab as opposed to those who were administered FOLFIRI plus bevacizumab or FOLFOX 4 plus either cetuximab or bevacizumab. It was also noted that both FOLFOX 4 and FOLFIRI exhibited a certain degree of toxicity, however, the specific side effects varied depending on the treatment regimen and the type of targeted therapy employed. It was concluded that FOLFIRI plus cetuximab was associated with the highest incidence of grade 3/4 adverse events [18]. In another safety analysis conducted by Watanabe et al., a comparison was made between FOLFOXIRI and FOLFIRI, in combination with either bevacizumab or panitumumab for the purpose of treating metastatic colorectal cancer. Their findings indicated that FOLFOXIRI, in combination with either bevacizumab or panitumumab, produced higher response rates, longer progression-free survival, overall survival, and greater rates of toxicity when compared to FOLFIRI with either drug. They suggested that FOLFOXIRI could potentially be a more efficacious treatment option for individuals with metastatic colorectal cancer, but it also carries an elevated risk of side effects [19]. In another clinical trial conducted by Colucci et al., it was determined that there was no statistically significant difference in the overall response rates between the two therapeutic regimens (31% for FOLFIRI and 34% for FOLFOX4, p=0.60). Additionally, the median progression time was found to be identical for both groups, lasting 7 months. However, the FOLFIRI treatment protocol was associated with a higher mortality rate within the initial 60 days of administration (2.8% vs 1.1% for FOLFOX4, p=0.24). The researchers reported that all patients were included in the analysis of treatment-related toxicities. Within arm A (FOLFIRI), there were two therapy-related deaths due to hematologic toxicity (febrile neutropenia), while another patient died of disseminated intravascular coagulation, which was not related to the treatment but occurred due to concomitant progressive disease [11]. Haong and colleagues discovered that FOLFOX 4 and FOLFIRI/FOLFOX 4 + cetuximab significantly extended both overall survival and progression free survival. Furthermore, the adverse events (grade≥3) and serious adverse events were comparable between treatments [20]. Ultimately, these results indicate that treatment selection must be based on individual circumstances, including the patient's overall health and the potential risks and benefits of the treatment. The present study exhibits a few limitations. Specifically, the small sample size poses a potential threat to the generalizability of the findings. Additionally, the follow-up period may not have been extensive enough to capture long-term outcomes, such as overall survival. Moreover, the study's inclusion criteria were restricted to patients with advanced colorectal cancer, thereby limiting the applicability of the findings to patients with early-stage disease. It is also noteworthy that the study solely compares FOLFOX 4 and FOLFIRI, without investigating other treatment options or combinations. Nevertheless, the present study's strength lies in its utilization of a randomized controlled trial design, which is a rigorous method to minimize bias and augment the validity of the findings. In future, further research studies should be conducted to investigate other treatment options and combinations and compare the long-term outcomes of different treatments.

CONCLUSIONS

There was no discernible disparity in the response rates observed between the two groups, albeit FOLFOX 4 demonstrated a marginally superior tumor control rate.

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However, FOLFIRI had a lower incidence of neutropenia, while FOLFOX 4 had a lower incidence of nausea and vomiting. These findings suggest that both regimens have similar efficacy but differ in their toxicity profiles.

Authors Contribution

Conceptualization: RK
Methodology: GH
Formal analysis: NA, AS
Writing-review and editing: TS, KA
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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