Comparison of Capox and Folfox with or Without Irinotecan in Colorectal Cancer

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Abstract- Colorectal cancer is cancer that occurs in the rectum or colon. Colon cancer and rectal cancer are often put together because they have many similar features. Colorectal cancer is one among the most common type of cancer and is also third in cancer-related mortality. Currently, Capecitabine and Oxaliplatin (CAPOX) and 5-fluorouracil, Leucovorin, and Oxaliplatin (FOLFOX) are one of the conventional adjuvant treatments of colorectal cancer. The aim of this study is to study the efficacy and safety profile of CAPOX (Capecitabine and Oxaliplatin) and FOLFOX (5-FU, Leucovorin and Oxaliplatin) along with or without the addition of Irinotecan. ***Result:*** A total of 158 subjects who received either CAPOX or FOLFOX were analyzed. Of these 158 subjects who were enrolled based on the inclusion and exclusion criteria, the percentage of subjects receiving FOLFOX was 62.6%, the percentage of subjects receiving CAPOX was 19.6%, and the percentage of subjects that received both CAPOX and FOLFOX was 17.7%, Also 20.2% of patients received irinotecan following administration of FOLFOX, 29% of patients received irinotecan following administration of CAPOX ***Conclusion:*** FOLFOX regimen was preferred than CAPOX in all age groups, including geriatric patients. Both these agents showed several adverse effects, but the ADR's associated with CAPOX is comparatively higher than with FOLFOX, and also ADR's were much higher when both these regimens were combined. Irinotecan is mostly preferred in stage IV of colorectal cancer. Combination of Irinotecan with CAPOX or FOLFOX seemed to improve the overall efficacy of the chemotherapeutic agents.

Index Terms- Colorectal Cancer, CAPOX, FOLFOX, Irinotecan

1. INTRODUCTION

Colorectal cancer occurs in the rectum or colon. They are also called cancer of the colon or the rectum, depending on where they arise. Colon and rectal cancer is paired together because they have several features in common. Cancer starts when the body's cells start growing out of control. Cells can turn tumorous in any part or site of the body and spread to other body parts. Colorectal cancers begin as growth on colon or rectum's inner lining. Those cultivations are called polyps. With time, some forms of polyps can transform into cancer (usually several years), but every polyp cannot become cancer. Colorectal cancer begins in the mucosa, which is the innermost layer and may grow outward through some other layers.[1] The high risk of developing colon and rectal cancer is due to the many studies "Westernized lifestyle," which means obesity, sedentary behavior, and foods rich in high-meat, high-calorie, and fat-rich. It was observed that dietary fat, which affects bacterial flora, influences colon cancer pathogenesis. [2]The two most major risk factors are alcohol consumption and tobacco smoking. In the survey done, it was seen that the drinkers who consume four or more drinks daily are at higher risk for developing cancer as this directly affects the folate synthesis.Smoking has been linked with the risk of developing colorectal adenoma. This causes the cigarette carcinogens in the circulatory system and gastrointestinal tract to spread, causing colorectal mucosa, increasing the risk of mutagenesis, inflammation, and carcinogenesis. [3] Based on the patient's health, size of the tumor, and its location. Surgery is the most treated option, and the type of surgery for cancer depends on the site of cancer cells and the extent of metastasis. Other treatment option includes radiofrequency chemotherapy, ablation, cryosurgery, targeted therapy, or radiation therapy. Stages I, II, and III cure, the

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intention is to eradicate the micro metastatic disease. Most stage IV disease is incurable; cancer growth is managed with palliative treatment, symptoms are decreased, quality of life improved, and survival increased. Systemic Chemotherapy palliates the symptoms and enhances the survival of unresectable disease patients. RT has the potential to control localized symptoms. Most mCRCs are incurable. Accepted initial chemotherapy regimens include oxaliplatin containing regimens (FOLFOX, CAPOX), irinotecan containing regimens (FOLFIRI), oxaliplatin, irinotecan, fluorouracil and leucovorin (FOLFOXIRI), infusion fluorouracil plus leucovorin, and capecitabine. However, randomized trials suggest that chemotherapy prolongs life and improves the quality of life. Once irinotecan is administered with fluorouracil plus leucovorin as the initial therapy, tumour response rates, time to progression, and OS increase. Early-onset diarrhoea and neutropenia are irinotecan dose-limiting toxicity. Combined with infusion fluorouracil plus leucovorin, oxaliplatin leads to higher response. Capecitabine monotherapy in patients who are unable to withstand IV chemotherapy is suitable for first-line treatment. It is required for oral administration, converted to fluorouracil in combination with oxaliplatin (CAPOX), and is a suitable replacement for infusion fluorouracil. [4]

2. LITERATURE REVIEW:

- Degirmencioglu et al. (2019) [5]

Patients receiving CAPOX were considerably older than those receiving FOLFOX. In the FOLFOX arm, the rate of progression of disease, metastasis and mortality was significantly higher than that of CAPOX arm. The overall survival rate was not much different between the two regimens. For older patients, the CAPOX regimen is preferred, the risk of development of the disease, metastasis, and mortality in FOLFOX is higher than in CAPOX.

- Jonathan et al. (2018) [6]

Both CAPOX and FOLFOX regimen are commonly used in the adjuvant therapy of colon and rectal cancer. Though their effects are assumed to be same they have not been compared directly. The study evaluated the toxicity profiles, survival, and RDI, associated with FOLFOX and CAPOX regimens. FOLFOX showed increased neutropenia and mucositis, CAPOX showed increased dose-limiting toxicity (DLT), CAPOX was also associated with increased diarrhoea and hand-foot syndrome. CAPOX, however, showed enhanced disease-free survival which remained an essential factor in high-risk patients. Hence the study showed that despite higher toxicities and lower relative dose intensity, CAPOX is associated with higher disease-free survival rate.

- Sombrero et al. (2018) [7]

The findings relied on the treatment and frequency of adjuvants. For CAPOX, three months regimen were as good as six months; for FOLFOX, an additional gain was applied to 6 months. Contrary to expectations, the low-risk patients benefited more from the six months than the high-risk group. The regimen choice and length will depend on the characteristics of the patient and the potential risk of a more lengthy procedure.

- Sánchez et al. (2018) [8]

Fluorouracil is still considered as one of the main drugs for metastatic colorectal cancer therapy; fluorouracil plus irinotecan (FOLFIRI), fluorouracil plus oxaliplatin known as FOLFOX regimen or fluorouracil plus Capecitabine known as CAPOX regimen are considered protocols for chemotherapeutical treatments producing outcomes that are similar. Another therapy involves these chemotherapy regimens in combination with novel molecular targeted drugs like bevacizumab, cetuximab or panitumumab. These chemotherapy regimens show significant survival benefits in some patients as either first- or second-line therapies—the factors affecting the decisions for a treatment option depending on the patient and toxicity of the drug.

- Prachi et al. (2017) [2]

The geographic variation in colorectal cancer incidence is known, and the study also shows a considerable difference in demographic and histological characteristics. India's more youthful population structure could contribute to the high number of patients presented at a young age. Further research is required into the higher number of signet ring tumours as compared to those identified in the West. Clinicians should be prepared to appreciate the significance of comprehensive family history,

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considering the large number of young patients diagnosed with CRC. The management strategy will also include dietary evaluation and therapy since most CRC patients are malnourished.

- Mamo et al. (2016) [9]

We present a real-life experience of patients being treated at two separate institutions with either mFOLFOX6 or CAPOX in the adjuvant environment, evaluating the dose strength and toxicity and their effect on patient outcomes. Our report shows that dose reductions in the CAPOX regimen do not appear to impact clinical outcomes in real-life practice.

- McLean et al. (2016) [10]

Currently, FOLFOX is considered the most common first-line agent and FOLFIRI the most common second-line and third-line agent for mCRC therapy. The study showed that bevacizumab is commonly used targeted therapy. Disease progression was the primary cause of Therapy discontinuation.

- Loree et al. (2014) [11]

Treatment for metastatic colon cancer uses either combination therapy or monotherapy with concurrent combination therapy. Therapy that patients undergo includes intravenous 5-fluorouracil (5-FU) therapy (FOLFOX) or Capecitabine administered orally with oxaliplatin (CAPOX). The study showed that Patients medicated with CAPOX had much lower doses of fluoropyrimidine and oxaliplatin compared with patients treated with FOLFOX who had higher-grade toxicity; however, the overall clinical outcomes did not worsen.

- Alessandra P and Alberto F 2007) [12]

We may draw a number of conclusions based on the available data regarding second-line therapy for advanced CRC. Chemotherapy of the second-line active agent is superior to only the best supportive treatment. After a 5-FU failure, the intense regimens include FOLFOX, Irinotecan, FOLFIRI and IROX with FOLFIRI being superior to IROX. In general, FOLFOX is the best choice after first-line treatment based on irinotecan, and the FOLFOX plus bevacizumab combination seems to be superior to FOLFOX given alone. FOLFIRI and Irinotecan are the most suitable choices following a FOLFOX failure. Cetuximab plus irinotecan should be an effective regimen.

3. MATERIALS AND METHOD:

Objectives:

The main objectives of this study are

- To compare the efficacy of CAPOX & FOLFOX with or without irinotecan in colorectal cancer.
- To compare the safety of CAPOX & FOLFOX with or without irinotecan in colorectal cancer.
- To identify the efficacy and safety of different treatment regimens other than CAPOX & FOLFOX in colorectal cancer.

Inclusion criteria:

- Patients with colon and rectal cancer.
- Patients of both gender.
- Geriatric patients.

Exclusion criteria:

- Incomplete medical records.
- Below 18 years of age
- Pregnancy

	CAPOX(n=31)	**FOLFOX(n=99)**	**CAPOX & FOLFOX(n=28)**
FEMALE	8	25	10
MALE	23	74	18

- Cancers other than colon and rectal cancer.

Study period:

This study is proposed to be conducted for a period of six months.

Sample size:

The sample size is expected to be around 150-200 patients

4. RESULT:

1. GENDER

In our prospective study, a total of 158 cases were collected in six months, of which 27% (43) were female patients, and 73% (115) were male.

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ADR	CAPOX(n=31)	FOLFOX(n=99)	CAPOX & FOLFOX(n=28)
Mouth ulcer	14(45.16%)	24(24.24%)	13(46.42%)
Hand foot syndrome	11(35.48%)	32(32.32%)	9(32.1%)
Anemia	14(45.16%)	50(50.50%)	12(42.85%)

2. AGE – WISE DISTRIBUTION:

Of the 158 patients that received treatment with CAPOX or FOLFOX, recording the age-wise distribution of subjects with a class size of 10 years, it was seen that majority of subjects belonged to the age group of 51-60, the mean age at the time of diagnosis was 55 years (range 25-78). In the CAPOX arm, the mean age was 55.1 years. In the FOLFOX arm, it was 53 years, and the Mean age for patients receiving both CAPOX and FOLFOX was 62 years.

3. STAGES OF COLORECTAL CANCER:

In this study, patients with stage –II, III, and IV colorectal cancer were only included. Of the 158 patients present at the time of our study, 34.2% had stage II colorectal cancer, 40.5% were in stage III colorectal cancer, and 25.3% in stage IV colorectal cancer. It was seen that in stage II and III, FOLFOX arm was more commonly preferred than CAPOX arm and in stage IV most of the patients received a combination of both CAPOX & FOLFOX.

4. TYPES OF COLORECTAL CANCER:

Of the 158 patients receiving treatment with CAPOX or FOLFOX, 36.7% were diagnosed with colon cancer, 22% were diagnosed with rectal cancer. 14% were diagnosed with rectosigmoid cancer, 3% were diagnosed with anorectal cancer, 24% of patients showed lung, liver, and bone metastasis.

5. ADVERSE EFFECTS:

Adverse effects like vomiting, pain, fatigue, Insomnia were commonly found in both CAPOX and FOLFOX arm. Other Adverse effects that were also seen in patients include mouth ulcers, hand-foot syndrome, and anaemia. Mouth ulcers were seen more in people taking a combination of CAPOX and FOLFOX and were also commonly found in patients who were administering only CAPOX. Hand-foot syndrome was mostly seen in CAPOX arm than in FOLFOX arm. On the other hand, anaemia was seen mostly in the FOLFOX arm compared to that of CAPOX arm.

6. EXISTING COMORBID CONDITIONS:

Any comorbid conditions present among the 158 patients were recorded and analysed. Most common comorbid conditions present among patients at the time of our study include inflammatory bowel disease, hypertension, diabetes, and coronary artery disease. Other existing conditions that were found were thyroid and asthma.

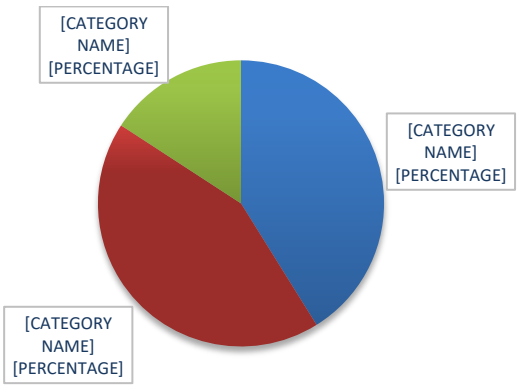
7. HISTOPATHOLOGICAL CHARACTERISTICS

Differentiation gives details of how little or how much tissue of a tumour looks like a normal cell. Well-differentiated cancer cells appear more closely like normal cells, and poorly differentiated cancer cells are likely to multiply. From the table, we can see that of the 158 cases collected, 41% of them had well-differentiated tumour cells, 43% were moderately differentiated, and 16% were poorly differentiated.

8. METASTASIS:

We found in our study that colon or rectal cancer mostly metastasizes to the lungs and liver. Of the 158 cases that were collected, 24 % showed metastasis to other regions of the body. Most of the patients diagnosed with metastatic colorectal cancer were given a combination of CAPOX and FOLFOX.

9. CAPIRI AND FOLFIRI:



In our study, 20.2% of patients received irinotecan following administration of FOLFOX, 29% of patients received irinotecan as following administration of CAPOX, and 64.2% of patients

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received irinotecan following administration of both CAPOX and FOLFOX.

10. TREATMENT DURATION:

The table shows the treatment duration of CAPOX and FOLFOX during our study; the average number of completed CAPOX cycles was eight; the average number of completed FOLFOX cycles was ten. Of patients receiving CAPOX, 44 per cent did not complete the standard eight cycles; of patients receiving FOLFOX, 70 per cent did not complete the standard twelve cycles.

5. DISCUSSION:

For our study, patient data were collected from the initial diagnosis to the chart review time. These data include medical history, disease stage, and tumour pathology at the time of diagnosis, chemotherapeutic regimens, duration of therapy, and type of surgery.

The study aims to assess the safety and efficacy profile of CAPOX- Capecitabine and Oxaliplatin, and FOLFOX-5-fluorouracil, Leucovorin, and Oxaliplatin, along with Irinotecan as adjuvant treatment in patients with colorectal cancer.

In our prospective study we observed that out of 158 patients that were diagnosed with colorectal cancer, 62.6% received FOLFOX (n=99), 19.6% received CAPOX (n=31) and 17.7% received both CAPOX & FOLFOX (n=28).

Of the 158 patients diagnosed with colorectal cancer, 115(73%) were male, and 43(27%) were female. FOLFOX is more commonly given than CAPOX in both male and female patients.

Of the 158 patients that received treatment with CAPOX or FOLFOX, the mean age at the time of diagnosis was 55 years (range 25-78). In the CAPOX arm, the mean age was 55.1 years; in the FOLFOX arm, it was 53 years, and the Mean age for patients receiving both CAPOX and FOLFOX was 62 years. Degirmencioglu et al. [5] conducted a study that showed that Patients who received CAPOX were older than those who were administered FOLFOX; however, in our study, we found that in most of the older patients a combination of both CAPOX and FOLFOX were received. (p=0.005)

We excluded patients with stage 0 and stage I colorectal cancer for our study because CAPOX and FOLFOX are not commonly preferred in the early stages of colorectal cancer; hence we only included patients with stage –II, III and IV colorectal cancer. Of the 158 patients present at the time of our study, 34.2% had stage II colorectal cancer, 40.5% were in stage III colorectal cancer, and 25.3% in stage IV colorectal cancer. We found that in stage II and III, FOLFOX arm was more commonly preferred than CAPOX arm, and most of the patients with stage IV of colorectal cancer received a combination of both CAPOX & FOLFOX.

Adverse events profile of FOLFOX and CAPOX regimens varies greatly among previous studies; Mamo et al. [9] reported that nausea and diarrhoea were more common in FOLFOX arm than in CAPOX arm. Loree et al. [11] found that diarrhoea and hand-foot syndrome were more frequent in CAPOX, Degirmencioglu et al. [5] found that hand-foot syndrome is more common in CAPOX arm than in FOLFOX arm. Nausea and diarrhoea were common in both arms. In our study, mouth ulcer and hand-foot syndrome were more common in CAPOX arm than in FOLFOX arm, Anaemia was more common in FOLFOX arm than in CAPOX arm, and other adverse effects like nausea, vomiting, fatigue, were common in both arms.

Degirmencioglu et al. [5] conducted a study that showed that CAPOX regimen was more commonly used among older patients because of existing comorbidities. In our study, we found no correlation between the treatment regimen and the existing comorbidities.

According to the study done by Degirmencioglu et al. [5] Development of metastasis is significantly higher in FOLFOX arm than in CAPOX arm. Our study found that the Development of metastasis is considerably higher in FOLFOX than in CAPOX.

NUMBER OF CYCLES:

FOLFOX (n=99)	CAPOX (n=31)
MEAN = 9.92	MEAN= 7.19
MEDIAN=10	MEDIAN= 8
% of cycles not completed= 70.7	% of cycles not completed=43.75

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The average number of cycles completed in CAPOX arm was 8 (range: 1–10 cycles) the average number of cycles completed for FOLFOX was 10 (range: 1–18 cycle). Among patients that received CAPOX, 43% did not finish the standard eight cycles; of patients receiving FOLFOX, 70.7% did not finish the standard 12 cycles at the time of our study. This result could be inconclusive because of the shorter duration of our study.

In the study performed by Guglielmi A et al. [12] found that Following FOLFOX failure, Irinotecan, and FOLFIRI are at present the most suitable option. In the study by Grothey et al. showed that administration of Irinotecan, along with FU-LV based therapy and oxaliplatin-based therapy, significantly improved the overall survival rate of the patient. In our study, we found that administering Irinotecan after administration of FOLFOX was 20.2%, administering Irinotecan after administration of CAPOX was 29 %, and administering Irinotecan to patients who received both CAPOX and FOLFOX was 64.2%.

The duration of our study is six months; at that time of our study, more than 98% of patients treated with either CAPOX or FOLFOX were still alive.

Limitations of the present study include its prospective nature, short duration, and the low rate of expected events

6. CONCLUSION:

In this study, the main aim is to evaluate the efficacy and safety profile of CAPOX (Capecitabine and Oxaliplatin) and FOLFOX (5-Fluorouracil, Leucovorin and Oxaliplatin) with or without the addition of Irinotecan in the adjuvant settings in patients with colorectal cancer. In this study, patient data, including initial diagnosis, medical history, disease state, tumour pathology, chemotherapeutic regimens, type of surgery, and duration of therapy, was collected.

Both CAPOX and FOLFOX regimens were compared, and it has been identified that FOLFOX regimen was preferred than CAPOX in all the age groups, including geriatric patients older than 60.

When it comes to the safety of these chemotherapeutic agents, both CAPOX and FOLFOX showed several adverse effects, but the ADR's associated with CAPOX is comparatively higher than with FOLFOX, and also ADR's were much higher when both these regimens were combined.

In most of the cases of high-risk colorectal cancer or stage IV colorectal cancer, this study has identified that a combination of CAPOX and FOLFOX was preferred rather than CAPOX or FOLFOX alone.

Irinotecan is mostly preferred in stage IV of colorectal cancer and administered in most cases in combination with FOLFOX and CAPOX. Combination of Irinotecan with CAPOX or FOLFOX seemed to improve the overall efficacy of the chemotherapeutic agents.

The efficacy of these regimens in this study could not be established due to short study duration, the reason being, efficacy for this study was based on two criteria, i.e. rate of metastasis and death, both of these criteria were inconclusive because the time duration was only six months. During this period, both CAPOX and FOLFOX were equally preferred.

7. ACKNOWLEDGMENT

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