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Original Article

Oxaliplatin Rechallenge (FOLFOX 4) versus (FOLFIRI) in Metastatic Colorectal Cancer Patients Pretreated with Oxaliplatin (FOLFOX 4)

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ABSTRACT

Background: For metastatic colorectal cancer, commonly used regimens are combinations of fluoropyrimidines such as 5-FU or capecitabine with either irinotecan or oxaliplatin, in addition to bevacizumab or antibodies against EGFR. There is no significant difference in terms of efficacy between FOLFIRI and FOLFOX and selection of one or the other regimen often depends on patients' comorbidities, institutional or personal preferences. After progression on first-line treatment, patients can benefit from the alternate regimen in second line. The optimal first-line regimen for metastatic colorectal cancer after oxaliplatin-containing adjuvant chemotherapy is not defined.

Aim: To compare the clinical outcomes of reintroducing FOLFOX 4 to the introduction of FOLFIRI after disease progression had occurred at least 1 year from the end of adjuvant treatment (FOLFOX 4).

Methodology: The current study is a prospective phase 3 study, which was done at Clinical Oncology and Nuclear Medicine Department, Ain Shams University Hospitals, during the period between Sept. 2015 and Nov. 2017, included a total number of 50 patients who were randomized into two equal groups, with locally recurrent and/or metastatic colorectal adenocarcinoma one year after adjuvant FOLFOX4, arm A was rechallenged with FOLFOX4, arm B received FOLFIRI. Institutional Ethical Committee approval was taken, the protocol was reviewed and approved by the Research Ethical Committee at the Faculty of Medicine, Ain Shams University on Sept. 2015.

Results: There is no significant difference as regard overall survival in both arms. In Arm A, median OS was 22.4 months vs 20.1 months in Arm B (P-value 0.728) with median follow up 25.5m. Regarding efficacy, the response varies among the two studies groups. In Arm A, the overall response rate (ORR) is 16% (4/25) and the disease control rate is recorded in 56% (14/25) of patients while in Arm B the ORR is 32% (8/25) and the disease control rate was recorded in 68 % (17/25) of patients. Median progression free survival 5.6 m in Arm A and 8.3 m in Arm B, with a significant difference (P-value0.024).

Conclusion: oxaliplatin rechallenge in mCRC offers anti-tumor activity in terms of tumor response rate, PFS and OS with manageable toxicity so the FOLFOX regimen is an appropriate comparator with other chemotherapy regimens used in treatment of advanced colorectal cancer.

Keywords
FOLFOX 4,
FOLFIRI,
mCRC

INTRODUCTION

Cancer colon is the second leading cause of cancer death among men and women combined and the third most commonly diagnosed cancer worldwide. It is estimated 135,430 new cases in 2017 and 50,260 estimated deaths in 2017. [1]

Although patients with early stage CRC commonly undergo potentially curative resection, disease recurrence may occur and is thought to arise from occult micrometastases that are present at the time of surgery. [2]

Despite embarking on adjuvant chemotherapy, approximately 30 -35% of the patients with stage III CRC eventually relapse. [3] Although some patients may have either an isolate metastasis or a local recurrence that is curable via surgery, most patients with metastatic CRC (mCRC) are incurable. The treatment in this setting generally consists of palliative chemotherapy with the goal of prolonging overall survival (OS) and maintaining quality of life. [4]

Treatment for mCRC would be exactly the same for patients previously exposed or not to adjuvant therapy. Many of those patients with recurrent disease in the modern era were already exposed to oxaliplatin during their adjuvant therapy. A question that remains unanswered is the role of retrying oxaliplatin-based chemotherapy for a patient who had already received it in the adjuvant setting and relapsed with metastatic disease. [5]

Aim of the Work

To compare the clinical outcomes of reintroducing FOLFOX 4 to the introduction of FOLFIRI after disease progression had occurred at least 1 year from the end of adjuvant treatment (FOLFOX 4).

Patients and Methods

The current study is a prospective phase 3 study which was done at Ain Shams University Hospitals Clinical Oncology and Nuclear Medicine Department, during the period between Sept. 2015 and Nov. 2017, included a total number of 50 patients who were randomized into two equal groups, each consisted of 25 patients with locally recurrent and/or metastatic colorectal adenocarcinoma. Institutional Ethical Committee approval was taken, and the protocol was reviewed and approved by the Research Ethical Committee at the Faculty of Medicine, Ain Shams University on Sept. 2015. Inclusion criteria were patients who have a histologically confirmed diagnosis of CRC, previously received FOLFOX 4 as adjuvant therapy at least 1 year before documented progression, age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, measurable or evaluable disease according to RECIST guidelines (Response Evaluation Criteria in Solid Tumours), neutrophil count ≥1,500/mm^3; platelet count ≥100,000/mm^3; hemoglobin ≥9.0 g/dL; total bilirubin ≤1.5 times the upper limit of normal; aspartate aminotransferase and alanine aminotransferase ≤3.0 times the upper limit of normal (≤5.0 if liver metastases were present); serum creatinine ≤1.5 times the upper limit of normal, and without any significant comorbidity nor other primary cancer.

CT chest and pelviabdomen with contrast was done to all patients before starting treatment, every 8 weeks during study therapy, and every 3 months during post therapy till disease progression, or till data analysis that took place after the last patient enrollment. Bone scan was done in case of clinical doubt (bone tenderness or elevated serum alkaline phosphatase level). Patients were assessed before each cycle by hematological, kidney and liver function tests.

Subjective symptoms, physical examination, performance status, and adverse reactions were recorded before starting the next treatment cycle. Measurable lesions were reassessed by the imaging used at baseline assessment and every 2 cycles.
After a signed informed consent, the patients were randomized into 2 arms to receive either:

Arm A: (FOLFOX)
The recommended dose schedule given every two weeks is as follows:
Day 1: Oxaliplatin 85 mg/m² followed by 5-FU 400 mg/m² IV bolus given over 2–4 minutes, followed by 5-FU 600 mg/m² IV infusion.
Day 2: Leucovorin 200 mg/m² IV infusion over 120 minutes, followed by 5-FU 400 mg/m² IV bolus given over 2–4 minutes, followed by 5-FU 600 mg/m² IV infusion as a 22-hour continuous infusion.

Arm B: (FOLFIRI)
The regimen consists of:
Day 1: irinotecan 180 mg/m² IV and leucovorin 200 mg/m² IV infusion followed by 5-FU 400 mg/m² IV bolus given over 2–4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W as a 22-hour continuous infusion.
Day 2: Leucovorin 200 mg/m² IV infusion over 120 minutes, followed by 5-FU 400 mg/m² IV bolus, followed by 5-FU 600 mg/m² IV infusion.

Adequate anti-emetic therapy before FOLFIRI infusion, antacids and steroids were ensured for all patients. Atropine was given for irinotecan-related cholinergic symptoms if needed.
Safety was evaluated in all patients who received treatment, and adverse event frequencies were recorded and graded in accordance with the Common Terminology Criteria for Adverse Events version 4.0.

Dose modification in the current study
In FOLFOX arm, the treatment was delayed about 1 week to permit the patient recovery from grade 3 neutropenia, only 3 patients developed persistent grade 2 neurotoxicity, where the treatment was delayed up to 2 weeks to allow patient recovery. 25% dose reduction was applied when the full dose was intolerable. One patient developed grade 3 neurotoxicity which was persistent although 25% dose reduction was applied so the discontinuation of oxaliplatin was considered at 5th cycle.

In FOLFIRI arm, the treatment was delayed up to 2 weeks due to grade 3 diarrhea in 5 patients.

The primary endpoint is to compare 2-year overall survival (OS) between the two arms, t**he secondary endpoints** are to compare disease control rate (DCR), overall response rate (ORR), progression-free survival (PFS), and toxicity.

Outcome assessment
Patients were evaluated clinically, radiologically and biochemically for those receiving chemotherapy.

Effects of treatment and toxicity reports: evaluation of response is done based upon the RECIST guidelines (Response Evaluation Criteria in Solid Tumours version 1.1 (Table 1). [6]

Table 1. Response definition according to RECIST criteria[6]

	Target lesions
Complete response (CR)	Disappearance of all target lesions and all nodes with short axis < 10 mm
Partial response (PR)	≥ 30 % decrease in the sum of target lesions taking as reference the baseline sum
Stable disease (SD)	Neither response nor progression
Progressive disease (PD)	≥ 20 % increase in the sum of target lesions taking as reference the smallest sum measured during follow-up (nadir) and ≥ 5 mm in absolute value

Table 2. Baseline demographic characteristics of study cases

Measure		Arm A	Arm B	P value
Age	Median	56	45	0.827
	Range	37-65	22-68	
Gender	Male	14 (56%)	17 (68%)	0.382
	Female	11 (44%)	8 (32%)	
Family History	Negative	21 (84%)	21 (84%)	1.00
	Positive	4 (16%)	4 (16%)	
Performance Status (ECOG)	PS 0	8 (32%)	4 (16%)	0.084
	PS 1	16 (64%)	15 (60%)	
	PS 2	1 (4%)	6 (24%)	
Smoking	No	15 (60)	16 (64%)	0.771
	Yes	10 (40%)	9 (36%)	
Sidedness	Rt. Colon	12 (48 %)	16 (64 %)	0.254
	Lt. colon	13 (52%)	9 (36 %)	
T Stage	T1	0	0	0.199
	T2	2 (8%)	1 (4%)	
	T3	22 (88%)	19 (76%)	
	T4	1 (4%)	5 (20 %)	
N Stage	N0	4 (16%)	4 (16%)	0.440
	N1	18 (72%)	16 (64%)	
	N2	3 (12%)	3 (12%)	
	N3	0 (0%)	2 (8%)	

Table 3. Patterns of adjuvant treatment failure

Measure		Arm A	Arm B	P value
Number of Metastases	One site	10 (40 %)	13 (52%)	0.446
	Two sites	9 (36%)	5 (20%)	
	Three Sites	6 (24%)	5(20%)	
	Four sites	0 (0%)	1 (4 %)	
	Five sites	0 (0%)	1(4 %)	
Liver metastases	None	12 (48 %)	18 (72 %)	0.08
	Hepatic mets	13 (52%)	7 (28%)	
Lung Metastses	None	19 (76 %)	15(60%)	0.225
	Lung mets	6 (24%)	10(40%)	
Non-loco regional Nodal involvement	None	16 (64 %)	19(76%)	0.354
	LN involvement	9 (36 %)	6(24%)	
Local Recurrence	None	14 (56%)	19(76%)	0.135
	Local Recurrence	11 (44 %)	6(24%)	
Other metastatic Sites	None	10 (40%)	9(36%)	0.7707
	Yes	15 (60%)	16(64%)	
CEA Baseline	Not Evaluated	4(16%)	4(16%)	1.000
	Normal	9(36%)	9(36%)	
	Increased	12(48%)	12(48%)	
CA 19.9 Baseline	Not Evaluated	6(24%)	4(16%)	0.643
	Normal	10(40%)	9(36%)	
	Increased	9(36%)	12(48%)	

Routine examination was performed at the first follow-up (6 weeks after completion of treatment) and thereafter every three months up to 2 years, performance status, weight and toxicity documentation was carried out at each follow up. Radiological evaluation 6 and 12 weeks took place after completion of treatment protocol, then every 3 months within the first year and 6 months thereafter.

Statistical analysis

The DCR was calculated from the number of patients who achieved a complete response (CR), partial response (PR), or stable disease with treatment, while the ORR was based on the number of patients who had CR or PR. PFS was defined as the interval between the date of starting treatment and the date of confirming disease progression or death. Data for patients without disease progression were censored on the date at which the patient was last confirmed to be alive. OS was calculated from the date of starting treatment until the date of death from any cause. In patients who were lost to follow-up, data were censored on the date when the patient was last confirmed to be alive. PFS and OS were estimated by the Kaplan–Meier method and were compared using the log-rank test, with predictive or prognostic factors being identified by univariate analysis. Multivariate analysis of the factors was conducted by using the Cox

Table 4. Over all response rate (ORR) in both arms

Measure	Arm A	Arm B	Chi-square	P
Complete response (CR)	0	3	1.754	0.185
Partial response (PR)	4	5		
Over all response rate (ORR)	4 (16%)	8 (32%)		

Table 5. Disease control rate (DCR) in both arms

Measure	Arm A	Arm B	Chi-square	P
Over all response rate (ORR)	4 (16%)	8 (32%)	0.764	0.382
Stable disease (SD)	10 (40%)	9 (36%)		
Disease control rate (DCR)	14 (56%)	17 (68%)		
Progressive disease (PD)	11 (44%)	8 (32%)		

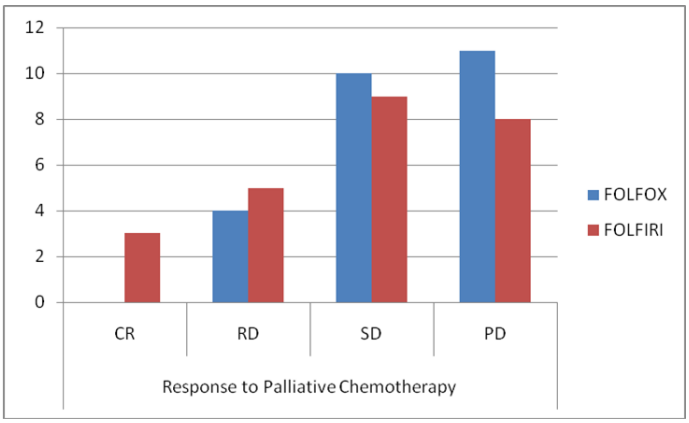

Figure 1. Disease control rate in Arm A (FOLFOX) Vs. Arm B (FOLFIRI).

Survival analysis in our study was done after median follow up 25.5m.
2- year overall survival rate for Arm A was 56% while 44% in Arm B.

There is non-significant difference as regard overall survival in both arms (P value: 0.728) (Chi-square statistic was 0.121)
In Arm A (FOLFOX): median OS was 22.4 months (95% CI 10.2–32.6) while mean OS was 17.432.

In Arm B (FOLFIRI): median OS was 20.1 months (95% CI 11.4–28.8) while mean OS was 16.748(figure 2).

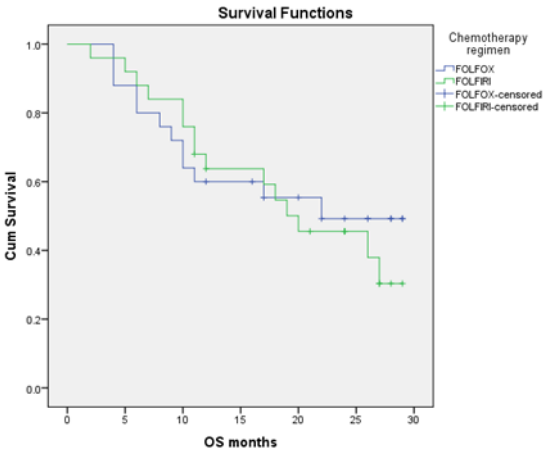

Figure 2. Median overall survival in both arms as in Kaplan- Meier curve.

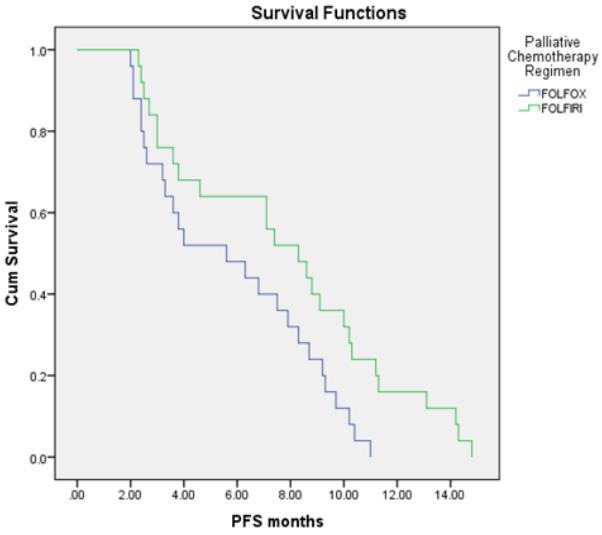

Figure 3. Median progression free survival (PFS) in both arms as in Kaplan- Meier curve

Regarding progression free survival**,** there is a significant difference as regards means and median progression free survival in both arms (P value: 0.024) (Chi-square statistic was 5.04)
In Arm A: median PFS was 5.6 months (95% CI 1.5–9.7) while mean PFS was 5.796; while in Arm B: median PFS was 8.3 months (95% CI 5.8–10.8) while mean PFS was 7.74 (figure 3).

The toxicity profile didn't differ markedly among the two arms with mild to moderate toxicity which increased the tolerability of both regimens. The only toxicity which had a significantly difference was diarrhea where it was more in Arm B (P value =0.006).

Table 6. Toxicities grades in both arms.

Toxicity	G0		G1		G2		G3	
Arm A	Count	%	Count	%	Count	%	Count	%
Neurotoxicity	13	52%	3	12%	8	32%	1	4%
Hand and Foot Synd.	19	76%	2	8%	3	12%	1	4%
Nausea	21	84%	2	8%	1	4%	1	4%
Vomiting	21	84%	2	8%	2	8%	0	0%
Diarrhea	23	92%	1	4%	1	4%	0	0%
Anorexia	17	68%	4	16%	4	16%	0	0%
Mucositis	22	88%	2	8%	1	4%	0	0%
Elevated Bilirubin	20	80%	3	12%	2	8%	0	0%
Alopecia	19	76%	3	12%	3	12%	-	-
Cardiac toxicities	20	80%	3	12%	2	8%	0	0%
Skin	20	80%	2	8%	2	8%	1	4%
Fatigue	20	80%	3	12%	1	4%	1	4%
Fever	20	80%	3	12%	2	8%	0	0%
Anemia	17	68%	5	20%	2	8%	1	4%
Neutropenia	19	76%	3	12%	2	8%	1	4%
Thrombo-cytopenia	19	76%	4	16%	2	8%	0	0%

Table 6. Toxicities grades in both arms (continued)

Toxicity	G0		G1		G2		G3		P-value
Arm B	Count	%	Count	%	Count	%	Count	%	
Neurotoxicity	20	80%	2	8%	3	12%	0	0%	0.096
Hand and Foot Synd.	19	76%	2	8%	4	16%	0	0%	0.767
Nausea	20	80%	2	8%	2	8%	1	4%	0.949
Vomiting	21	84%	2	8%	1	4%	1	4%	0.721
Diarrhea	12	48%	2	8%	6	24%	5	20%	0.006
Anorexia	20	80%	3	12%	2	8%	0	0%	0.591
Mucositis	20	80%	1	4%	4	16%	0	0%	0.328
Elevated Bilirubin	20	80%	3	12%	2	8%	0	0%	1.000
Alopecia	17	68%	3	12%	5	20%	-	-	0.737
Cardiac toxicities	21	84%	1	4%	3	12%	0	0%	0.542
Skin	19	76%	3	12%	2	8%	1	4%	0.973
Fatigue	20	80%	2	8%	2	8%	1	4%	0.991
Fever	20	80%	2	8%	3	12%	0	0%	0.819
Anemia	17	68%	5	20%	2	8%	1	4%	1.000
Neutropenia	18	72%	4	16%	3	12%	0	0%	0.713
Thrombo-cytopenia	18	72%	3	12%	4	16%	0	0%	0.658

Discussion

For metastatic colorectal cancer, commonly used regimens are combinations of fluoropyrimidines such as 5-FU or capecitabine with either irinotecan or oxaliplatin, in addition to bevacizumab or antibodies against EGFR. There is no significant difference in terms of efficacy between FOLFIRI and FOLFOX and selection of one or the other regimen often depends on patients' comorbidities, institutional or personal preferences. After progression on first-line treatment, patients can benefit from the alternate regimen in second line. However, these clinical trials were performed when oxaliplatin was not yet accepted as part of standard adjuvant chemotherapy. Therefore, the optimal first-line regimen for metastatic colorectal cancer after oxaliplatin-containing adjuvant chemotherapy is not defined. [8]

In the retrospective study carried by **Moreau and his colleagues** [8], as regard patient age, it ranged between 37 and 65 years with median age 56 years in Arm A (FOLFOX) while in Arm B (FOLFIRI) the age ranged between 22 and 68 years with median age 45 years.

The median age in **our study** was younger than the western countries studies. This may be due to unique features of the pathogenesis of colorectal cancer in Egypt as evidenced by the conclusion from the epidemiologic studies by **Soliman et al.** [9] where the percentage of colorectal cancer was high in young patients.

Moreau and his colleagues [8] study showed 19 males (59.5%) and 13 females (50.5%).

José and his colleagues [10] study showed 11 (50%) patients were male and (50 %) were females.

In our study, the total number of males was 31 (62 %) while the total number of females was 19 (38 %).

The difference in gender percentage in the previous studies may have no significance as the patients were randomly selected.

José and his colleagues [10] study showed 4 patients (18.2%) had score 0, 16 (72.7%) patients were score 1 and score 2 in 2 patients (9.1 %).

Suenaga and his colleagues [11] studied 28 patients (84.8%) with score 0 and 5 patients (15.8%) with score 1.

Our study was consistent with the rates of other studies as regard PS because the patients were selected to have ECOG PS 0 to 2 as criterion to be enrolled in the study.

Mayer RJ and his colleagues[12] reported 19.5 m median OS for FOLFOX arm versus 15 m for FOLLFIRI Arm with median follow up 20.4 m. this study showed a significant difference (P value 0.0001).

Second-line chemotherapy likely contributed to overall survival and may explain the higher median OS in FOLFOX arm. Because oxaliplatin was not readily available and because irinotecan was marketed in North America, more patients received irinotecan after discontinuing FOLFOX than received oxaliplatin after discontinuing IFL. This is consistent with our study where median OS showed no a significant difference between both arms (P value 0.728) (22.4 m for Arm A versus 20.1 m for Arm B with median follow up 25.5 m).

In our study, twelve % of patients reached CR in FOLFIRI arm while in Tournig and and his co-workers[6] study where there is 5% of patients reached CR in FOLFIRI arm VS 3% in FOLFOX arm which explained by the surgical metastatectomy. Tournigand and his co-workers[6] reported that the ORR and DCR were 56% and 79% with FOLFIRI (95% CI, 47% to 65%) versus 54% and 81% with FOLFOX6 respectively (95% CI, 45% to 63%; *P* was not significant) which is consistent with our study where the ORR and DCR were 32% and 68% with FOLFIRI versus 16% and 56% with FOLFOX6 respectively with no significant difference (P value =0.303) and with Colucci and his co-workers[7] study who showed that the ORR and DCR were 34% and 75.6 % with FOLFIRI versus 36% and 74.3 % with FOLFOX6 respectively (*P* value =o.7).

The second-line therapies may have an impact on survival. In our study (OS was 20.1 m for FOLFIRI vs 22.4 m FOLFOX), Tournig and and his colleagues[6] reported that OS was 15m for FOLFIRI vs 19.5 m FOLFOX and Chibaudel and his colleagues[13] reported that OS was 21.5m for FOLFIRI vs 20.6m FOLFOX, where In our study, second-line therapy was administered to 64% of the FOLFIRI arm and to 76% of the FOLFOX4 arm. In Chibaudel and his colleagues study, second-line therapy was administered to 74% of the FOLFIRI arm and to 62 % of the FOLFOX4 arm. In Goldberg and his colleagues[14] study, second-line therapy was administered to 67% of the FOLFIRI arm and to 75 % of the FOLFOX4 arm.

In Colucci and his colleagues[7] study, overall toxicity was mild in both patient groups; grade 3 to 4 toxicities were uncommon in both arms, with no statistical difference. Our study found also significant statistical difference as regard diarrhea (8 % in Arm A vs 52 % in Arm B with P value =0.006) and overall, toxicity was mild in both patient groups; grade 3 to 4 toxicities were uncommon in both arms, with no statistical difference. In Colucci and his colleagues[7] study, only eight patients experienced grade 3 neuropathy, which was reversible in all patients and did not require discontinuation of treatment. The median number of FOLFOX4 cycles administered in this study was eight, and this justifies the observed low rate of neurosensory toxicity. With the same regimen in de Gramont [15] study, 18% of patients experienced grade 3 neurologic toxicity, 10% of patients had grade 2 to 3 neuropathy after three and nine cycles of FOLFOX4, 25% had grade 2 to 3 neuropathy after eight and 12 cycles, and 50% had grade 2 to 3 neuropathy after 10 and 14 cycles. Furthermore, with an enhanced dose of OHP and with a higher median number of cycles, severe neurologic toxicity occurred in 34% of patients treated with the FOLFOX6 regimen, and 19% of patients had grade 3 neuropathy at the beginning of FOLFIRI second-line therapy.

In Douillard and his colleagues[16] study, there were no significant differences in toxicities between the two regimens except neurotoxicity which is higher in arm B (P-value 0.003). The most frequently recorded grade 3/4 toxicity was diarrhea in both treatment arms, followed by bone marrow toxicity in both arms, and peripheral neuropathy in arm B only. The main difference with the previous studies is the no significant difference as regard neurotoxicity in our study (P-value 0.096) which may be due to the adverse effect of oxaliplatin that is cumulative and dose-dependent. In Douillard and his colleagues[16] study neurotoxicity is due to the cumulative toxicity from OXA (The median numbers of treatment cycles 3 (1–7) in FOLFOX arm) while in our study (The median numbers of treatment cycles 2 (2–6) in FOLFOX arm).

Difference of the results of our study and other studies is due to the short time of follow up and due to some patients missed follow up.

Conclusion

Oxaliplatin rechallenge in mCRC offers anti-tumor activity in terms of tumor response rate, PFS and OS with manageable toxicity so the FOLFOX regimen is an appropriate comparator with other chemotherapy regimens used in treatment of advanced colorectal cancer.

Recommendations

The results of the present study suggest that it would be better to be applied on larger number of patients, to be multi-centric for better results, for better assessment survival and better quality of life assessment. Longer follow up period is strongly recommended.

The concept of "selected patient" must be well defined. Obviously, further studies are needed to better define the prognostic information allowing them to become important criteria to select patients who will benefit from the rechallenge treatment available.

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