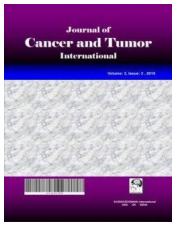

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Metronomic Low Dose Leucovorin- Fluorouracil versus Supportive Treatment for Patients with Recurrent or Metastatic Colorectal Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: There was an improvement in therapeutic regimens for advanced colorectal cancer (CRC) in the last few decades. The low dose metronomic palliative chemotherapy in patients with advanced CRC after the failure of standard chemotherapy led to a dramatic increase in efficacy, reduction of mortality rates, and improves survival in the form of control symptoms, and enhances or improves quality of life which is an important issue in that group of patients.
Patients and Methods: We include 60 Patients with recurrent or metastatic colorectal cancer after failure of multiple lines of chemotherapy. The patients were randomized in two groups either to receive supportive treatment in group A (30 patients) or low dose weekly leucovorin 20 mg/m² plus 5-flourouracil 425 mg/m² for 3 weeks and 1 week rest in group B (30 patients). Patients in group B received palliative chemotherapy for 4 months at least.
Results: After a follow up period of 19 months, the mean time to progression (TTP) is 4.9 months for the group (A) but is higher in group (B) as it is 7.8 months and it shows a statistically significant difference (P value <0.001). Also, the mean overall survival(OS) is 15.3 months for group (A) and 18.8 months for group (B) and this is statistically significant (P value <0.002). No grade 3 or 4

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toxicity was detected. After 4 months of the study, 29 patients (96.6%) still have the stable disease compared to 18 patients (60%) of group (A). After 8 months, only 12 patients (40%) of group (B) show stable disease while all patients of group (A) have disease progression.
Conclusion: We conclude that metronomic weekly leucovorin-5 FU could provide a good tolerable way to go on with chemotherapy treatment while at the same time not have major threatening side effects.

Keywords: Metronomic chemotherapy; metastatic colorectal cancer; metastatic rectal cancer; low dose chemotherapy.

1. INTRODUCTION

Worldwide, colorectal cancer (CRC) is considered as a major cause of morbidity and mortality and represented the 3rd most common cancer [1]. Actually, more than half of the patients will develop metastasis and die from this cancer. Many protocols of chemotherapy are given for those patients with recurrent or metastatic colorectal cancer after failure of adjuvant settings. Patients who developed progression after many lines of chemotherapy protocols usually stop their treatment and just continue under best supportive care (BSC). However, many cases still able to tolerate further treatment and can have some benefits from low dose chemotherapy [2].

In the contrary of conventional chemotherapy, low dose metronomic chemotherapy is discovered to act by special different mechanisms and theories. One of them; The low dose metronomic chemotherapy has been used as a cancer dormancy therapy due to the chemotherapeutic drugs may have high depressive effects on the host immunity with the usual high doses and so can't be tolerated by the patient. Another one; is that stimulation of the immune system is believed to be initiated by suppression of regulatory T-cells (T-regs) and activation of dendritic cells. Suppression of T-regs lead to activation of tumour unspecific and tumour-specific effector cells while activation of dendritic cells is thought to enhance the immune stimulatory effect [3,4]. The other mechanisms of metronomic chemotherapy are to control the tumour by primary target tumour angiogenesis. Angiogenesis is the process in which new blood vessels are formed. The anti-angiogenic effect is thought to be mediated by killing the bone-marrow-derived endothelial progenitor cells or by either killing or inhibiting the endothelial cells in the vasculature of the tumour [4]. It has also been proved that metronomic chemotherapy might enhance the effect of target drugs such as the monoclonal antibody like the bevacizumab [5].

There was an improvement in therapeutic regimens for advanced CRC in the last few decades. The low dose metronomic palliative chemotherapy in patients with advanced CRC after failure of standard chemotherapy led to a dramatic increase in efficacy, reduction of mortality rates, and improves survival in the form of control symptoms, and enhances or improves quality of life which is important issue in that group of patients [6,7].

The aim of this study is to compare the effect of low dose metronomic chemotherapy versus supportive treatment for cases of recurrent or metastatic CRC regarding time to progression (TTP) and overall survival (OS) for those who was received multiple lines of chemotherapy previously but failed and to assess toxicity profile of the metronomic chemotherapy group.

2. MATERIALS AND METHODS

In this trial, we include 60 Patients with recurrent or metastatic colorectal cancer after failure of multiple lines of chemotherapy. They presented to the Clinical Oncology and Nuclear Medicine Department in the period from January 2017 till July 2018 at Mansoura University Hospital (MUH).

All patients were confirmed pathologically to have grade II & III adenocarcinoma of the colon or the rectum and received previous chemotherapy (2 or 3 lines) after surgery and adjuvant treatment for metastatic disease or recurrent disease. The patients were randomized in two groups either to receive supportive treatment in group A (30 patients) or palliative low dose chemotherapy by weekly leucovorin 20 mg/m² plus 5-flourouracil 425 mg/m² for 3 weeks and 1 week rest in group B (30 patients). Patients in group B received palliative chemotherapy for 4 months at least. Supportive care introduced to the patients in group (A) was defined as any line of treatment rather than chemotherapy and includes symptoms control by pain relief, localized palliative radiotherapy,

palliative surgery, transfusion of blood, and psychosocial support.

All patients have performance status grade 1 or 2 according to ECOG performance scale. All participants who receive chemotherapy must have adequate haematological readings, serum total bilirubin and creatinine to allow chemotherapy cycles. Toxicity assessments for the chemotherapy group were gained. The primary assessment was assessed by common terminology criteria for adverse effects (CTCAE) version 4.0. The primary endpoints were TTP and OS in both treatment study groups.

2.1 Statistical Analysis

SPSS version 22 was used for data analysis. Firstly, Shapiro test was used to test the normality of data. Number and percent were used to describe qualitative data. Chi-square test used to test the association between categorical variables while Fischer exact test was used when expected cell count less than 5.

For parametric data, continuous variables were presented as mean ± SD (standard deviation). The Student *t* test was used to compare the two groups.

For survival analysis, Kaplan-Meier test was used and statistically significant differences among curves were tested by Log-Rank test.

Level of Significance:

The limit of significance is fixed at 5% (p-value) for all the above listed statistical tests.

We consider the results:

- Non-significant when the probability of error is more than 5% ($p > 0.05$).
- Significant when the probability of error is less than 5% ($p \leq 0.05$).

The results will be more significant when we obtain a much smaller p-value.

3. RESULTS

A total of 60 patients, all with a pathological diagnosis of recurrent or metastatic CRC, were included in this study in the period from January 2017 till July 2018. The patients were randomized in two groups either to receive supportive treatment in group A (30 patients) or metronomic palliative low dose chemotherapy in group B (30 patients) by weekly leucovorin 20 mg/m² plus 5-flourouracil 425 mg/m² weekly for three weeks and then one week rest.

In Table 1, we show the baseline characteristics of the patients. The mean age is comparable between both groups it is 48.9 (±7.3) years in group (A) and 47.6 (±7.7) years in group (B) and there is no statistically significant difference between both of them (p-value: 0.48). Both groups are balanced as regard sex distribution and no statistically significant difference between both of them (p-value: 0.795). The primary site of the tumour was equally weighted between both groups and mostly half of the patients were colon cancer and the other half were rectal cancer with no statistical difference between both groups (p value: 0.796). As regard patients' performance status, our patients in both groups were either ECOG 1 or 2 with no significant difference statistically (p value: 0.791) (Table 1).

Our patients in group (A); 6 of them received 2 previous lines of chemotherapy after failure of adjuvant treatment (Folfiri and Xeloda after the failure of adjuvant Folfox) and the rest of this group received 3 lines of treatment (Folfox, Folfiri and Xeloda) after failure of adjuvant Mayo clinic protocol. While the group (B), received 2 lines of chemotherapy in 10 patients and 3 lines in 20 patients with no significant differences between both of them.

In group (A) 29 patients were died by the end of the study, one patient still survive and in group (B) only 2 patients are survived and the remaining 28 patients died.

The chemotherapy treatment in group B is tolerable as regard haematological and gastrointestinal side effects. No grade 3 or 4 toxicity was detected and no need to stop treatment due to complications of chemotherapy.

The primary endpoints of this study are TTP and OS. After a follow up period of 19 months, the mean TTP is 4.9 months for group (A) but is higher in group (B) as it is 7.8 months and it shows a high statistically significant difference (P value <0.05*) as shown in Fig. (1). Also, the mean OS is 15.3 months for group (A) and 18.8 months for group (B) and this is highly statistically significant (P value 0.05*) as shown in Fig. 2.

Table 1. Patients characteristics among the studied groups

Patients characteristics	Group A (n=30)	Group B (n=30)	Test of significance	p-value
Age/years			t=0.707	0.483
Mean ± SD	48.93±7.31	47.56±7.67		
Min-Max	37-63	28-61		
Sex			χ^2 =0.067	0.795
M	14 (46.7%)	13 (43.3%)		
F	16 (53.3%)	17 (56.7%)		
Site			χ^2 =0.067	0.796
Rectum	14 (46.7%)	15 (50%)		
Colon	16 (53.3%)	15 (50%)		
Performance status			χ^2 =0.071	0.791
1	11 (36.7%)	12 (40%)		
2	19 (63.3%)	18 (60%)		
Number of previous lines of chemotherapy			χ^2 =1.36	0.243
2	6 (20%)	10 (33.3%)		
3	24 (80%)	20 (66.7%)		
Outcome			χ^2 =2.46	0.292
Survived	1 (3.3%)	2 (6.7%)		
Died	29 (96.7%)	28 (93.3%)		

*t: student t-test, χ^2 : chi square test, FET: Fischer exact test,*significant p <0.05*

After 4 months of the study, which is the least period of treatment for group (B), 29 patients (96.6 %) still have stable disease compared to 18 patients (60 %) of group (A). after 6 months, 24 patients (80 %) of group (B) compared to 12 patients (40 %) of group (A) still non progressed. After 8 months, only 12 patients (40%) of group (B) still show stable disease while all patients of group (A) have disease progression.

4. DISCUSSION

Treatment of metastatic colorectal cancer depends mainly on chemotherapy. The use of conventional chemotherapy protocols is limited by many factors such as the tumour cells heterogeneity, the suppression of anticancer immune response and the microenvironment exerting a protective action [8].

Table 2. Side effects among group B

Variables	Group B (n=30)
Haemato-suppression	4 (13.3%)
Diarrhoea	5 (16.7%)
Mucositis	4 (13.3%)
Nausea & vomiting	3 (10%)

Table 3. Kaplan-meire time to progression among the studied groups

	Estimate	Std. error	95% confidence interval		Log rank test	p- value
			Lower bound	Upper bound		
Group (A)	4.967	0.260	4.456	5.477	37.3	<0.05*
Group (B)	7.867	0.270	7.337	8.396		
Overall	6.417	0.265	5.897	6.936		

Table 4. Kaplan-Meire overall survival among the studied groups

	Estimate	Std. error	95% confidence interval		Log rank test	p- value
			Lower bound	Upper bound		
Group (A)	15.395	0.670	14.082	16.707	9.56	0.05*
Group (B)	18.857	0.574	17.732	19.982		
Overall	16.882	0.542	15.821	17.944		

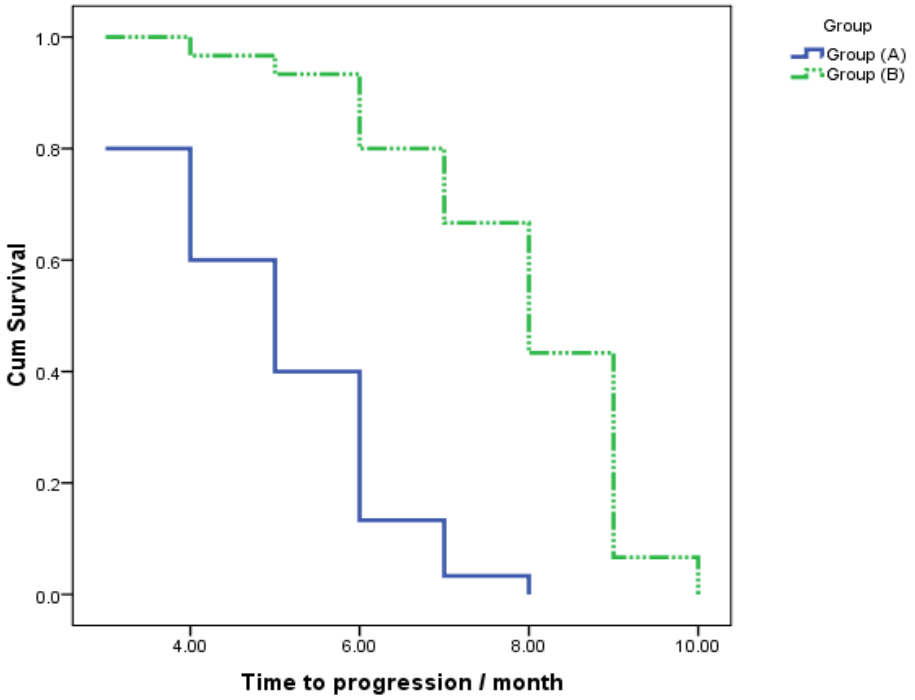

Fig. 1. Kaplan-Meire time to progression among the studied groups

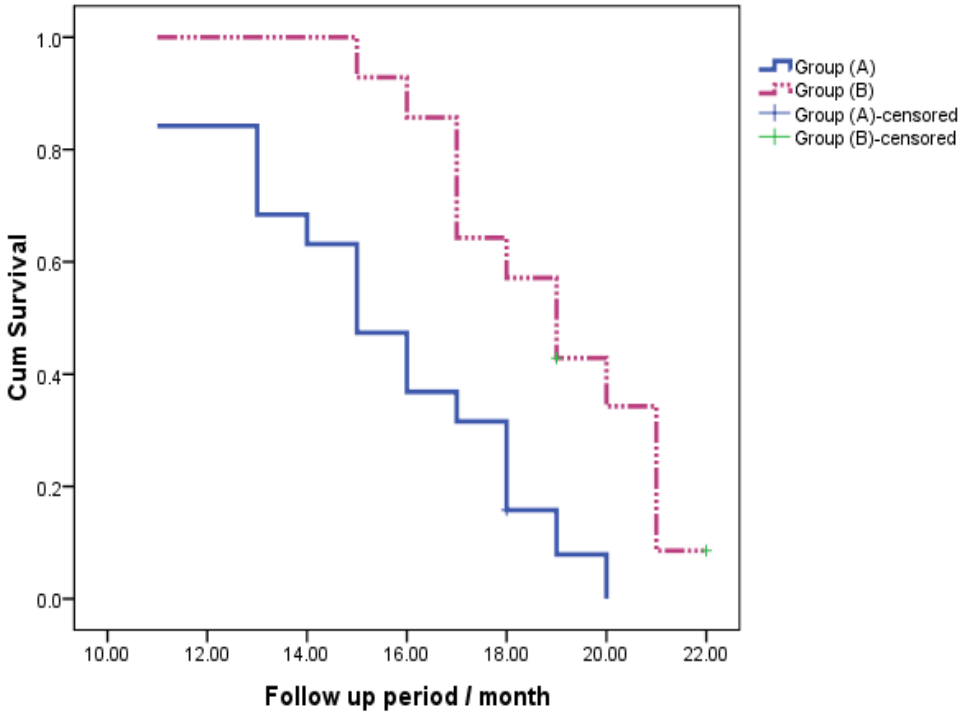

Fig. 2. Kaplan-meire overall survival among the studied groups

Metronomic chemotherapy uses chemotherapy with lower doses, given at smaller interval periods and without interruption, creating a continued cytotoxic action on the malignant cells leading to a regressive effect on the tumour [9].

Because of low doses of cytotoxic drugs, metronomic schedules have shown a good tolerable effect, with a lower rate of severe adverse effects compared to conventional protocols [10].

In our study we choose low dose weekly leucovorin, 5-flurouracil alone regimen because it is well-tolerated protocol, with a good toxicity profile, the cost of the therapy was suitable and the weekly based regimen introduces a solution to give the treatment while monitoring toxicity at the same time. Patients who planned for this metronomic protocol should be pretreated with a failed two or three lines of chemotherapy.

We selected the TTP as a primary endpoint to study to which extent the metronomic therapy can control the disease. The mean TTP was 7.8 month in the metronomic group (B) compared with 4.9 months in supportive care only group (A). This result was statistically significant with p value less than 0.05.

There was also OS benefit with metronomic leucovorin-5FU, the mean OS was 18.8 months compared to the 15.3 months in the supportive care group which is statistically significant.

A low incidence of toxicities with low dose leucovorin-5 FU and without any grade 3 or 4 adverse events is encouraging the finding of our study results. Our data are matched with the reflection of previous experiences and studies showing that metronomic protocols are generally well tolerated with a low occurrence of severe major side effects.

Only a few studies used metronomic protocols of oral fluoropyrimidines in CRC. The benefit of these studies was noticed. In one trial, sixty-eight patients with recurrent cancer colon after 2 or 3 lines of chemotherapy were treated with low dose oral capcitabine. The median OS was 8 months. The overall disease control rate was 26%, partial response (PR) in 2 patients (3%) and stationary disease (SD) in 14 patients (23%). Nineteen percent of patients were free from progression events for at least 6 months. There were no cases of grade 4 side effects or treatment-related mortalities. They concluded that metronomic capcitabine was moderately effective and well tolerated in pretreated patients with recurrent CRC [11].

Also In a phase II study, low dose capcitabine was used together with anti-inflammatory drug celecoxib in advanced cancer patients. They found that it was a well-tolerated continuous treatment using the combination of capcitabine and celecoxib, producing antiangiogenic effects, and had antitumor activity [12].

Another phase II study evaluated metronomic chemotherapy using cyclophosphamide in association with UFT plus celecoxib in heavily pretreated patients with advanced gastrointestinal cancers. A total of 38 patients were studied, and among them, 30 patients (79%) had a diagnosis of metastatic CRC. Patients received cyclophosphamide 500 mg/m² IV on day 1 and from day 2 oral cyclophosphamide 50 mg/d plus UFT 100 mg/bid and celecoxib 200 mg/bid until disease progression or intolerance. The median PFS and OS were 2.7 and 7.1 months, respectively after a median follows up period of 18.3 months. As regard safety profile, metronomic cyclophosphamide plus UFT and celecoxib resulted in only grade 1 toxicities [13].

Other studies investigated different metronomic chemotherapy protocols. One trial studied metronomic irinotecan in resistant or refractory cases to chemotherapy in metastatic CRC patients. Twenty patients received a continuous infusion of irinotecan. The median PFS was 2.07 months, and median OS was 8.4 months after a median follow up period of 20 months. No side effects much more than grade 1 were observed, and no haematological side effects occurred. The results of this study suggested that metronomic irinotecan in resistant or refractory metastatic CRC patients to chemotherapy could have a potential antitumor effect without major side effects [14].

A randomized phase II study in advanced cancer patients that exhausted all effective therapies under standard care, evaluated the effect and safety of metronomic cyclophosphamide or megestrol acetate. A total of 88 patients were randomized to administer oral metronomic cyclophosphamide or megestrol acetate till disease progression or toxicity. Twenty-five percent of patients were suffering from CRC, while the remaining 75% of patients were lung cancer, soft tissue sarcoma, melanoma, bladder

cancer, gastric cancer, and hepatic carcinoma patients. Two months of progression-free rate (PFR) was 9% in the megestrol acetate group versus 20% in the metronomic cyclophosphamide group. This study concluded that only metronomic cyclophosphamide seems to be effective and safe in the treatment of pretreated patients with advanced solid cancers [15].

5. CONCLUSION

Finally, we conclude that our study can support the possible role of metronomic leucovorin, 5-flourouracil as a salvage metronomic chemotherapy for excessively pretreated CRC patients with a good performance status. Metronomic weekly leucovorin-5 FU could provide a good tolerable way to go on with chemotherapy treatment while at the same time not provide major threatening side effects.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

The study has the approval of the IRB committee of the Faculty of Medicine (MFM-IRB), Mansoura University, Egypt. The code number is R.19.02.431.R1.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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