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Comparative study of metronomic capecitabine and oxaliplatin versus classic XELOX in Egyptian metastatic colorectal cancer patients

Raghda Y. Abu El-Ela[1]✉, **Mostafa M. El-Serafy**[2], **Maha Yahia**[2], **Mervat M. Omran**[4], **Rasha Allam**[3], **Samia A. Shouman**[4]

[1]Clinical Oncology Department, Faculty of Medicine, Fayoum University, Egypt
[2]Medical Oncology Department, National Cancer Institute, Cairo University, Egypt
[3]Department of Medical Statistics, National Cancer Institute, Cairo, Egypt
[4]Pharmacology, Unit, Cancer Biology Department, National Cancer Institute, Cairo University, Egypt

✉**Corresponding author**
Clinical Oncology Department,
Faculty of Medicine, Fayoum University,
Egypt
Email: raghda_yahia@yahoo.com / raghdayahia12@gmail.com

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ABSTRACT

Background: In Egypt, colorectal cancer (CRC) is a diagnosis of advanced tumors. While the drastic survival gains with standard doses of chemotherapy have significant toxicity in certain CRC patients. Less than the maximum tolerated dose of chemotherapy, with no prolonged drug-free breaks, tumor progression is impeded. Therefore, a safer alternative to standard dose therapy with a safer toxicity profile would be. *Methods:* This is a Phase II randomized study which included 70 (35 in each arm) metastatic Egyptian CRC cancer patients diagnosed at the National Cancer Institute of Egypt. Patients were treated with either classic XELOX (arm A) or capecitabine (2000 mg daily x 8 weeks) and oxaliplatin (30 mg / m2 weekly X 8 weeks) followed by 2 weeks of rest (arm B). Both therapies continued until the disease progressed or were tolerated. Toxicity and analysis of survival were recorded after two years. *Results:* The mean PFS was 7.6 months for patients receiving Arm A, while patients receiving the arm B was 5.7 months (*P=0.318*). Median OS for arms A & B were nearly equal (15.9 m &15.8m) (*P = 0.8*). Disease control rate was slightly higher in arm A (48%) than arm B (37%) (P=0.3). Most toxicity was higher in group A (P-values: anemia 0.03, diarrhea 0.027, hand & foot syndrome 0.002, neutropenia 0.001, oral mucositis 0.003, and gastritis 0.004). Also, higher grade III toxicities in arm A; anemia, hand and foot syndrome, diarrhea, fatigue, gastritis (P-values: 0.017, <0.001, 0.009, <0.001, <0.0001) respectively. *Conclusion:* Metronomic protocol had significantly lower rates of most toxicities and grade III ones than standard protocol with equal OS, the use of metronomic treatment did not affect PFS or response rates.

Keywords: colorectal cancer, metronomic, capecitabine, XELOX, Egyptian patients.

1. INTRODUCTION

The introduction of metronomic chemotherapy (MC) opened avenues for the development of oral, inexpensive, and well-tolerated treatments that might prevent tumor progression for an extended period of time (André et al., 2014). Although MC was initially reported to act through anti-angiogenic mechanisms, additional anticancer properties have since been unveiled. These include the stimulation of the antitumor immune response and prevention of stromal activation. Thus, MC is now regarded as a form of multi-targeted therapy. MC can be rationally combined with targeted and/or immunological therapies (Chan et al., 2016). Metronomic chemotherapy was described as chemotherapy at minimally toxic doses without prolonged drug-free breaks. MC can induce tumor stabilization or tumor responses in patients with cancer that were refractory to previous lines of treatment or relapsed after conventional chemotherapy (Sarmiento et al., 2008; Sterba et al., 2006).

Clinical trials demonstrated that MC, either alone or in combination, was well tolerated. Rarely have high-grade toxic effects. Common side effects of MC were grade 1 nausea and/ or vomiting, Grades 1 and 2 of anemia, neutropenia, leukopoenia and lymphopenia, and weak fatigue (Reardon et al., 2009). Fluorouracil (5-FU) is the backbone of the chemotherapeutic regimens used in advanced colorectal cancer in first- and second-line settings. It can be administered as an infusion or bolus, with infusion having less marrow suppression. Capecitabine, an oral prodrug of 5-FU, has equal efficacy to 5-FU. Diarrrhea is the main side effects of infusional 5-FU. Capecitabine has comparatively much higher incidence of diarrhea, mucositis and hand-foot syndrome (Rothenberg et al., 2008). Capecitabine is one of heavily tested drugs in metronomic protocols, due to easiness of intake, variability in dosing modifications, manageable side effects and lack of liver toxicity.

The aim of the study is to test if low metronomic dose chemotherapy with Capecitabine (Cap) and Oxaliplatin (Ox) is as effective as classic XELOX in treatment of metastatic colorectal cancer (mCRC) as regards clinical response, toxicity and survival.

2. PATIENTS AND METHODS

Design and sampling

This is a randomized phase II prospective study that included 70 metastatic colo-rectal cancer patients diagnosed at National Cancer Institute (NCI), Cairo University between January 2016 and December 2018. In-depth analyses were provided to study patients receiving XELOX (2 arms: standard & low dose) and have valid treatment and follow up information. Seventy Patients with metastatic colo-rectal cancer were randomized to be treated with either:

Arm A: Classic XELOX: Capecitabine 1000mg/m2 BID P.O. day 1-14 with (OX)
130mg/m2 on day1, cycle to be repeated every 21days.

Arm B: (Cap) 2000mg fixed dose daily, (OX) 30mg/m2 weekly X8 week's then 2weeks rest.

- Primary End Point: toxicities and grades
- Secondary end point: Response rates, Progression free survival at two years, overall survival

Inclusion criteria & data

Patient age 18-70 years of both sexes, with PS 0-2 and pathologically proven mCRC with unresectable metastases (rectal cancer is also included). They should have observable lesions (which can be measured accurately with calipers or ruler in at least one dimension, and measure must be at least 20 mm using conventional techniques or 10 mm using spiral CT scan) and No previous treatment for metastatic disease and had ended adjuvant treatment > 6 months Also, peripheral neuritis less than grade 2. Normal functions of the organ: (Creatinine ≤1.2, Bilirubin ≤1.2, SGOT/SGPT< 2N, HB >9gm/dl, WBC>3.5/dl with ANC >1.5/dl, Plat ≥100/dl) Bilirubin should not be > 2.5N for patients with liver metastases, and not > 5N for transaminases. (All patients were screened for HCV and HBS Ag by PCR) and adequate cardiac functions (EF>50%). Patients with only ascites, effusions bone metastases were not eligible.

Response assessment

Response rates: according to response evaluation criteria in solid tumors (RECIST version 1.1) (appendix A).
Toxicities & grades: according to common terminology criteria for adverse events v5.0 (US NCI, 2017) (appendix B).
Progression free survival: (calculated from date of start of therapy till date of progression according to RECIST).
Overall survival: (calculated from date of diagnosis to date of death).

Statistical method

Data management and statistical analysis were performed using Statistical Package for Social Sciences (SPSS) vs. 21. Numerical data were summarized using means and standard deviations or medians and ranges, while categorical data were summarized as percentages. Comparisons between the 2 groups with respect to normally distributed numeric variables were done using the t-test while those, non-normally distributed, were compared by Mann-Whitney test. For categorical variables, differences were analyzed with chi square test and Fisher's exact test when appropriate. Kaplan and Meier procedure were used to estimate the overall survival rates and progression free rates and comparisons between the different prognostic factors were done using the Log rank test. For PFS; patients who did not progress or die were censored at the last evaluation before the loss to follow-up then significant variables were entered into the Cox Proportional Hazards Model. All p-values are two-sided. P-values < 0.05 have been deemed significant. An intention to treat analysis was done with no interims.

3. RESULTS

Clinic-pathological characteristics & types of recorded toxicities for each group: A total of 70metastatic CRC patients belonging to Egyptian population were enrolled in this study (35 patients in each group). Table (1) shows the clinic pathological characteristics of each group.

Table 1 clinic pathological characteristics of each group

Factors	Arm (A) (number, %)	Arm (B) (number, %)	P-value
Age			
<=50	22 (62.9)	17 (48.6)	0.229
>50	13 (37.1)	18 (51.4)	
Positive family history	2(5.7)	2 (5.7)	---
Comorbidities			
Diabetes	3 (8.6)	10 (28.6)	0.031
Hypertension	4 (11.4)	4 (11.4)	1.000
PS			
I	13 (9.1)	21 (60)	0.068
II	7 (20)	14 (40)	
Complaint			
Abdominal pain Bleeding per rectum Diarrhea Constipation Weight loss	13 (37.1) 11 (31.4 5 (14.3) 3 (8.6) 3 (8.6)	17 (48.6) 9 (25.7) 4 (11.4) 5 (14.3) -----	
Duration of symptoms			

<=3	20 (57.1)	24 (68.6)	0.322
>3	15 (42.9)	11 (31.4)	
Site of the tumor			
Left side	23 (65.7)	26 (74.3)	0.714
Right side	6 (17.1)	4 (11.4)	
Transverse	4 (11.4)	5 (14.3)	
Multicentric	2 (5.7)	----	
No of metastatic sites			
1	16 (45.7)	24 (68.6)	---
2	17 (48.6)	9 (25.7)	
3	2 (5.7)	2 (5.7)	
Histological type			
Adenocarcinoma	23 (94.3)	31 (88.6)	0.673
Mucin secreting	2 (5.7)	4 (11.4)	
Pathological grade			
1	7 (20)	6 (17.1)	0.470
2	12 (34.3)	17 (48.6)	
3	16 (45.7)	12 (34.3)	
Obstruction	8 (22.9)	7 (20)	0.771
Elevated tumor markers	23 (65.7)	29 (82.9)	0.101
Increased TLC	6 (17.1)	11 (31.4)	0.163
Decreased Hemoglobin	12 (34.3)	13 (37.1)	0.803

The median duration of the treatment for arm A was 6 months (range: 2-8 months), for arm B, the median was 5 months (range: 2-10 months). Nearly all of the patients for both arms were compliant to receive the treatment (82.9% of arm A and 85.7% of arm B) while the rest of them were not (17.1% & 14.3% of arm A&B respectively).Toxicity occurred in 26 cases (75 % of arm A) and 21 cases (60% of arm B). Anemia, diarrhea, hand & foot syndrome, neutropenia, oral mucositis, fatigue, gastritis and abdominal pain were significantly higher in group A than group B (P-values: 0.03, 0.027, 0.002, 0.001, 0.003, 0.03, 0.004, 0.048) respectively. Most of grade III toxicities were significantly recorded in arm A whereas a smaller proportion of them recorded in arm B. The significant recorded grade III toxicities were anemia, hand and foot syndrome, neuropathy, fatigue, gastritis and abdominal pain (P-values: 0.017, <0.001, <0.001, <0.001, <0.0001, 0.019) Grade IV toxicities were not recorded in each arm. Treatment delay due to toxicity was recorded in 57.1% of cases in arm A while it was recorded with a less extent in cases receiving arm B (28.6%) as most of the affected part of them had grade I or grade II toxicities that were properly tolerated by the patients and managed by concomitant supportive care (Table 2).

Table 2 Types of the recorded toxicities for each group

	Arm A N=35 (100%)	**Arm B N=35 (100%)**	**P-value**
Toxicity recorded	26 (75%)	21 (60%)	0.203
Treatment delay	20 (57.1%)	10 (28.6%)	0.016
Types & grades of toxicity			
Anemia (n=34)	22 (65%)	12 (35%)	0.030
G I & II	9	10	---
G III	13	2	0.017
Diarrhea (n=43)	26 (60%)	17 (40%)	0.027
G I & II	4	9	---
G III	22	8	0.009
Hand and foot syndrome (n=33)	23 (70%)	10 (30%)	0.002
G I & II	3	10	---
G III	20	0	<0.001
Hepatotoxicity (n=22)	13 (59%)	9 (41%)	0.303
G I & II	6	4	---

G III	7	5	1.000
Neutropenia (n=16)	14 (88%)	2 (12%)	0.001
G I & II	5	2	---
G III	9	0	---
Oral mucositis (n=19)	15 (79%)	4 (21%)	0.003
G I & II	4	2	---
G III	11	2	---
Peripheral Neuropathy (n=41)	24 (59%)	17 (41%)	0.089
G I & II	1	12	---
G III	23	5	<0.001
Fatigue (n=31)	20 (65%)	11 (35%)	0.030
G I & II	3	10	---
G III	17	1	<0.001
Thrombocytopenia (n=7)	6 (17.1%)	1 (2.9%)	0.198
G I & II	6	1	---
G III	---	---	---
Gastritis (n=40)	26 (86%)	14 (14%)	0.004
G I & II	2	9	---
G III	24	5	<0.0001
Abdominal pain (n=44)	26 (59%)	18 (41%)	0.048
G I & II	8	12	---
G III	18	6	0.019

Responses for each group and its correlation to different toxicities

Of patients receiving arm A and arm B, the proportion of cases achieving SD (14.3% & 8.6%), PR (34.3%& 28.6%) and PD (51.4%& 62.9%) respectively (table 3).

Table 3 Response rates according to RECIST criteria

Response	ALL	Arm A No=35 (100%)	Arm B No=35 (100%)	P-Value
PR	22 (31.4%)	12 (34.3%)	10 (28.6%)	
SD	8 (11.5%)	5 (14.3%)	3 (8.6%)	
PD	40 (57.1%)	18 (51.4%)	22 (62.9%)	0.334
DCR (PR+SD)	30 (42.9%)	17 (85.7%)	13 (37.2%)	

Survival

Progression free survival (PFS)

The median PFS for patients receiving arm A was 7.6 months while the patients receiving arm B had median PFS 5.7 months (P=0.318) that was statistically insignificant (Table 4) (Figure 1). The use of metronomic strategy did not affect PFS.

Table 4 PFS of both groups

	Arm A No=35 (100%)	Arm B No=35(100%)
Events	31	31
Median PFS (m)	7.6	5.7
	P=0.809	

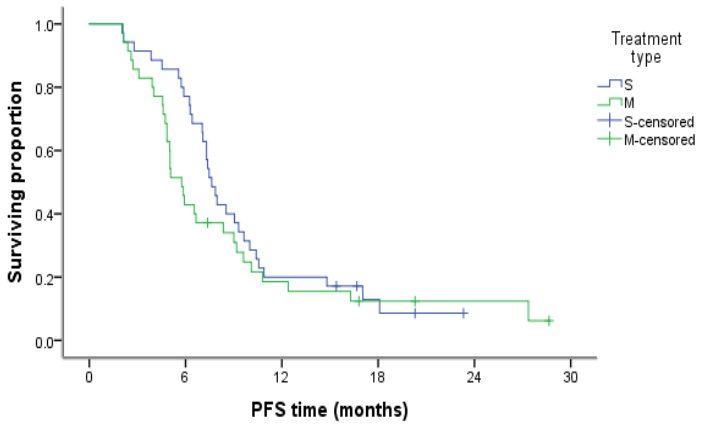

Figure 1 PFS in each arm

Overall survival

The median overall survival in arm A was 15.85 months that was nearly equal to arm B (15.82 months) and was statistically insignificant (P=0.809) Figure (2), Table (5). The OS was identical in both arms.

Table 5 OS in both arms

	Arm A No=35 (100%)	**Arm B No=35(100%)**
Events	23	20
Median OS	15.85	15.82
	P=0.809	

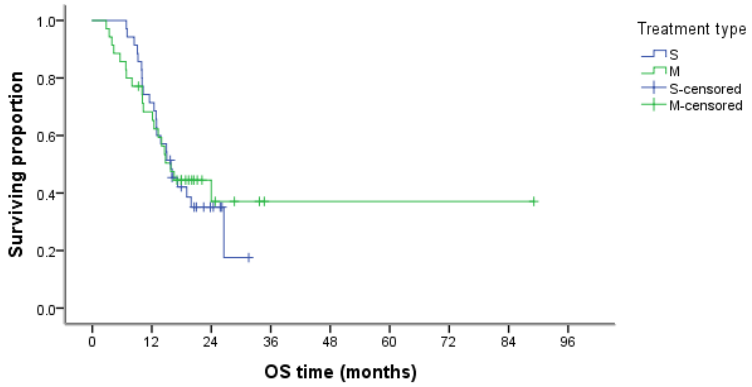

Figure 2 OS in each arm

4. DISCUSSION

Colorectal cancer (CRC) is a major health burden worldwide. There is wide geographical variation in incidence among the different countries (Wang et al., 2015). Approximately 55 % of the cases occur in more developed countries (Favoriti et al., 2016). In Egypt, like most of the developing countries, colorectal cancer incidence is lower than that of developed countries. It is the 7th ranked cancer representing about 4% of total cancers in both males and females (Ibrahim et al., 2014). Colorectal cancer is a disease predominantly affecting older individuals, but recent evidences suggest a constantly rising incidence in young age (Wang et al., 2015). In the United States, about 11% of colon cancers are occurred in individuals younger than 50 years (Ahnen et al., 2014).

The median age of patients included in the current study was 50 years which is similar to most Egyptian series as reported by El-Minia registry and in Gharbiah district, Egypt (51 & 53 years respectively) (Ibrahim et al., 2014). Our patients were younger compared to patients included in Japanese (Murata et al., 2016) and Canadian (McKay et al., 2014) studies (median was 63 and 73 years

respectively). Male gender was the dominant in many studies including CRC patients from Egypt, South Asia, Japan, USA and Canada (Ibrahim et al., 1014; de Silva et al., 2000; Murata et al., 2016; Li Q et al., 2014; McKay et al., 2014). However, in the current study, female gender was dominant which was similar tothat reported by Cancer Pathology Registry, National Cancer Institute (Mokhtar et al., 2016).

The presenting symptoms of CRC patients in our study were abdominal pain followed by bleeding per rectum in comparison to those of other studies with rectal bleeding being the commonest symptom (Ganapathi et al., 2011; de Silva et al., 2000). The prevalence of comorbidities among colorectal cancer patients in this current study were (Diabetes and Hypertension) contrary to Van Leersum studies indicated that hypertension and cardiovascular diseases were most prevalent comorbidities. In this study, a family history of colorectal cancer was reported in 4 (5.7%) of cases, a figure which is similar to 5.4% and 4.3% reported by (Chalya et al., 2013b) in Tunisia and (Azadeh et al., 2007) in Iran. This suggests genetic factors can play a significant role in this disease's development in our country. Findings from this study also showed that the commonest site of the tumor was the left side, followed by the right side. This is similar to findings in a retrospective study by (Abdalla et al., 2007) in Sudan but contrasts with the right-side preponderance (proximal shift) reported (Guraya and Eltinay, 2006) in Saudi Arabia and in developed countries (Takada et al., 2002). Adenocarcinoma was the most common histological type followed by mucin-secreting tumors accounting for (91.4% & 8.6%) of the cases. These findings were higher than that reported with studies by (Missaoui et al., 2010; Chalya et al., 2013a).

Approximately 35% of colorectal cancer (CRC) patients present with stage IV metastatic disease. Stage IV CRC carries a dismal prognosis: the 5-year survival rate for stage IV CRC is less than 10% (Jemal et al., 2012; Goldberg et al., 2007). The median survival time without chemotherapy in patients with stage IV CRC is approximately 5 months. In metastatic CRC, chemotherapy is used mainly with palliative intent. It improves the quality of life and prolongs longevity compared to the best supportive treatment. Until a few years ago, 5-fluorouracil (5-FU) modulated with folinic acid was the reference first-line treatment option for metastatic CRC, with objective response rates of 10-25% and manageable toxicity (Folprecht et al., 2004). Now, Combination chemotherapy regimens including irinotecan and oxaliplatin in combination with 5-FU, with or without a biological agent, have improved response rates to as high as 50% and overall survival times to 15-20 months (Jemal et al., 2012).

Our analysis included stage IV metastatic colorectal cancer cases with measurable lesions from a single center and all patients were treated with palliative chemotherapy only, (oxaliplatin in combination with capecitabine-the oral prodrug of 5-FU). The median OS was similar between both groups about 15 months which is similar to that reported in previous studies (Mitry et al., 2004; Douillard et al., 2000). Carreca et al. proposed a metronomic schedule for the treatment of elderly people with colorectal cancer (CRC), to reduce severe toxicity (primary endpoint) and to improve patient compliance, named M-COB (oxaliplatin 65 mg/m2 plus bevacizumab 7.5 mg/kg on day 1, and capecitabine at a fixed dose of 1000 mg bid, delivered from day 2 to day 15 every 3 weeks for 12 cycles) a median PFS of 12.3 months and an average OS of 23.5 months, higher than that recorded in our study, probably due to increased sample size and concomitant use of targeted therapy. No patients experienced grade 4 toxicity, the same as that observed in our study (Carreca et al., 2011).

5. CONCLUSION

In the metastatic setting advances are leading to a better understanding of CRC as a collection of multiple subtypes distinguished by their molecular profile. Chemotherapy is somehow changing the perspective concerning the best long-term management of primary CRC complications, prolongation, disease control and better quality of life. Clinical evidence supports the use of metronomic chemotherapy as an alternative treatment in cancer therapy. The main characteristics of this therapy are: the low toxicity and high anti-angiogenic activity, which translates in long duration of clinical benefit.

Metronomic regimens could in future be an alternative for patients with the burden of multiple health problems, in whom standard doses of chemotherapy cannot be used. In addition, metronomic chemotherapy can find its place as a maintenance treatment with equal benefit in clinical response and survival. Metronomic protocol was associated with lower rates of toxicity with nearly equal improvement in PFS or OS than standard protocol. Capecitabine remains an important therapeutic strategy in colorectal cancer patients due to its oral formulation, ease of dose modifications and administration in patients with liver dysfunction, and the lack of cumulative toxicities.

Future preclinical and clinical studies are needed to define the best agent to use according to tumor type, the number of agents, the doses of each agent to be used alone or in combination, and the timing of drug administration.

Trial NIH number

NCT04425564

Ethical approval for human

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Egyptian National Cancer Institute and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (ethical approval number: IRB00004025).

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Conflict of Interest

The authors declare that they have no conflict of interest.

Informed consent

Written informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Peer-review

External peer-review was done through double-blind method.

Data and materials availability

All data associated with this study are present in the paper.

Appendix

Part 1 Response evaluation criteria in solid tumors version 1.1

Target lesions

CR	disappearance of all target lesions, confirmed at 4 weeks.
PR	≥30% decrease of the sum of the longest diameter/s compared with the baseline.
PD	≥20% increase in the sum of the longest diameter of the target lesion over smallest sum observed, or appearance of new lesions.
SD	Neither PR or PD criteria met.

CR: complete response PR: partial response PD: progressive disease SD: stationary disease

Part 2 Common terminology criteria for adverse events version 5.0

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse events.

ADL: Activities of daily living

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