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Metronomic capecitabine as maintenance treatment after first line induction with XELOX for metastatic colorectal cancer patients

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Abstract

Maintenance treatment after first-line chemotherapy for patients with metastatic colorectal cancer (mCRC) is a priority strategy. However, which medicine is chosen is controversial. This study aimed to determine the efficacy and safety of maintenance treatment with metronomic capecitabine vs observation.

In this randomized controlled trial, patients who completed 18 weeks of induction chemotherapy with XELOX and achieved disease control were randomly assigned centrally (1:1) to receive maintenance therapy with metronomic chemotherapy or observation until disease progression. The primary endpoint was progression-free survival from randomization; secondary endpoints included overall survival and safety. Analyses were performed by intention to treat.

Between January 1st, 2017 and December 31th 2018, 48 patients were enrolled and randomly assigned to receive maintenance treatment with metronomic capecitabine (n = 25) or only observation (n = 23). The median progression-free survival in the metronomic capecitabine group was 5.66 (95% confidence interval [CI] 5.25–6.07) months vs 3.98 (95%CI 3.71–4.24) months in the observation group (hazard ratio 0.11, 95% [CI] 0.04–0.26, $P = .000$). There was no statistically significant difference in median overall survival: 23.82 (95% CI 22.38–25.25) months in the metronomic capecitabine group vs 21.81 (95% CI 20.23–23.38) months in the observation group (hazard ratio 0.49, 95% CI 0.21–1.11, $P = .087$). Subgroup analyses were generally consistent with the primary finding. Similar safety profiles were observed in both arms. The most frequent adverse events in metronomic capecitabine group included neutropenia, diarrhea, hand-foot skin reaction, and mucositis.

Maintenance therapy with metronomic capecitabine can be considered an alternative option following first-line chemotherapy of XELOX in patients with metastatic colorectal cancer with controlled toxicities.

Abbreviations: AEs = adverse events, CI = confidence interval, HR = hazard ratio, mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression-free survival, PR = partial remission.

Keywords: capecitabine, colorectal cancer, maintenance treatment, metronomic chemotherapy

1. Introduction

Colorectal cancer is one of the most common malignancies, with a morbidity of approximately 100 million cases per year.[1] About 20% of patients have already reached distant metastases at the time of diagnosis.[2] The first-line treatments for patients with metastatic colorectal cancer (mCRC) usually involve combination chemotherapies that include 5-fluorouracil and leucovorin plus either irinotecan or oxaliplatin.[3] The addition of bevacizumab or cetuximab (wild type KRAS, NRAS, and BRAF) to chemotherapy regimens improves overall survival (OS) or progression-free survival (PFS).[4] Because of the high cost of treatment, some patients in northern China chose only combined chemotherapy as their treatment option.

The cumulative toxicities of oxaliplatin often require the discontinuation of the drug and decrease patients' quality of life. Maintenance periods or treatment breaks are a frequent strategy in the management of mCRC patients.[5] Clinical studies evaluating the relative impact of maintenance with bevacizumab in combination with fluoropyrimidine when compared with a treatment break evidenced a significant improvement in PFS with a less relevant magnitude of benefit in terms of OS.[6–8] Some studies have explored the possibility of single-agent capecitabine as maintenance therapy after first-line chemotherapy in mCRC, with the result that maintenance therapy with single agent of

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capecitabine has a significantly longer PFS, favorable OS, and more acceptable toxicity than that of observation.[9–11]

Metronomic chemotherapy refers to either the constant (daily, multiple times a week, or weekly) or continuous administration of low-dose cytotoxic drugs without extended interruption.[12] The drugs used were usually inexpensive oral chemotherapeutic agents.[12] Studies have shown clinical efficacy with a lower toxicity profile than the maximum tolerated dose chemotherapy.[13] Even the same chemotherapeutic agents that were used in maximum tolerance dose (MTD) of chemotherapy showed efficacy when administered again through the metronomic method.[14] Some results from various studies have suggested that metronomic capecitabine had a favorable effect in terms of response rate and progression-free survival.[15–18] In terms of colorectal cancer, there are other studies evaluating the value of metronomic chemotherapy, including capecitabine[19–22]; however, the results have been controversial.

Above all, this study was designed to assess the efficacy and safety of metronomic capecitabine as a maintenance therapy, compared with observation, in patients achieving disease control with induction chemotherapy.

2. Materials and methods

This study was designed to evaluate the efficacy and safety of maintenance treatment with metronomic capecitabine vs observation after 18 weeks of induction chemotherapy with XELOX in mCRC patients. Inclusion criteria included the following: age ≥18 years; histologically confirmed adenocarcinoma of the colon or rectum; at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumor (RECIST, version 1.0); Eastern Cooperative Oncology Group Performance Status ≤2; a life expectancy of more than 3 months; adequate hematologic, hepatic and renal function. Exclusion criteria included severely toxic effects caused by capecitabine in induction chemotherapy, planned radical resection of all metastatic disease, unresolved bowel obstruction, central nervous system metastases, clinically significant cardiovascular disease within 1 year before randomization, active uncontrolled infection, uncontrolled diabetes mellitus, a history of neurological or psychiatric disorders. All patients were provided with written consent before treatment and consented to the use of their treatment process data for future medical research. This study was approved by the Second People's Hospital of Lianyungang' review boards and ethics committees (NO. 2017–019-01) after a careful review of the ethical and scientific characteristics of the study.

2.1. Randomization

Eligible patients were randomly assigned (at a 1:1 ratio) to receive either capecitabine (500 mg bid) or only observation. Randomization was done centrally by a sealed envelope system. The maintenance treatment was continued until disease progression, unacceptable toxicity, planned surgery, serious protocol violation, or patient withdrawal.

When patients occurred grade 3/4 AEs first time, they required a capecitabine dose reduction to the first level (75% of the total predicted dose). And then, if patients occurred grade3/4 AEs second time, they required a second capecitabine dose reduction (50% of the total predicted dose). If patients experienced grade 3/4 AEs third time, metronomic capecitabine treatment discontinued.

2.2. Assessment

Medical history, physical examination, and routine blood analysis (hematology and biochemistry) were performed within 1 week after study entry. A standard clinical laboratory work-up was performed at baseline and every 3 weeks thereafter. Imaging studies of measurable lesions were assessed within 28 days of study entry and repeated every 3 months during the maintenance treatment, or at any time when progression of the disease was suspected, or when study treatment was prematurely discontinued.

Disease control was defined as complete remission, partial remission, and stable disease. PFS was defined as the time between the start of the treatment and disease progression or death or last tumor evaluation. OS was considered as the duration from the start to the date of death or the last day of follow-up.

Adverse events (AEs) were recorded from registration until the end of the final study visit. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

2.3. Statistical analysis

The PFS and OS after treatment were estimated by the Kaplan-Meier method. The comparison of subgroup analysis was applied using a log-rank test. The hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were estimated using the Cox proportional hazards regression model, and the results were displayed in a forest plot. We also used Cox proportional hazards regression model to investigate whether the effect of primary treatment was modified by adjustments for various covariates. AEs were aggregated in the form of frequency counts and percentages.

All statistical analyses were performed using SPSS for Windows (version 20, IBM, Armonk, NY).

3. Results

3.1. Patient characteristics and treatment administration

Between January 1st 2017 and December 31th 2018, 48 patients were enrolled and randomly assigned to receive maintenance treatment with metronomic capecitabine (n=25) or only observation (n=23). One patient in the observation group was excluded because of incorrect information. Baseline demographic and clinical characteristics were balanced between 2 groups (Table 1). The median duration of follow-up at time of this analysis was 22 months (interquartile range 18–24).

3.2. Efficacy

The median PFS in the metronomic capecitabine group was 5.66 (95%CI 5.25–6.07) months vs 3.98 (95%CI 3.71–4.24) months in the observation group (HR 0.11, 95%CI 0.04–0.26, $P=.000$) (Fig. 1A). All patients in the 2 groups had progressed at the time of analysis.

There was no statistically significant difference in median OS, which was 23.82 (95% CI 22.38–25.25) months in the metronomic capecitabine group and 21.81 (95% CI 20.23–23.38) months in the observation group (HR 0.49, 95% CI 0.21–1.11, $P=.087$) (Fig. 1B). By May 1st 2020, 12 (54.5%) of the 22 patients in the observation group and 12 (48%) of the 25 patients in the metronomic capecitabine group had died.

Table 1

Baseline characteristics.

	Observation group (n, %)	Maintenance group (n, %)	*P* value
Age			.775
<65	15 (68.2)	18 (72.0)	
≥65	7 (31.8)	7 (28.0)	
Gender			.949
Male	13 (59.1)	15 (60.0)	
Female	9 (40.9)	10 (40.0)	
ECOG PS			.956
0	6 (27.3)	7 (28.0)	
1,2	16 ((72.3)	18 (72.0)	
Site of primary tumor			.798
Right	8 (36.4)	10 (40.0)	
Left	14 (63.6)	15 (60.0)	
Histology			.758
Well	5 (22.7)	5 (20.0)	
Moderate	10 (45.5)	14 (56.0)	
Low	7 (31.8)	6 (24.0)	
Metastatic time			.949
Metachronous	13 (59.1)	15 (60.0)	
Synchronous	9 (40.9)	10 (40.0)	
Number of metastatic sites			.302
<2	9 (40.9)	14 (56.0)	
≥2	13 (59.1)	11 (44.0)	
Response to induction treatment			.626
CR + PR	9 (40.9)	12 (48.0)	
SD	13 (59.1)	13 (52.0)	
Resected primary tumor			.730
Yes	13 (59.1)	16 (64.0)	
no	9 (40.9)	9 (36.0)	
Serum lactate dehydrogenase			.344
Normal	10 (45.5)	8 (32.0)	
Above normal	12 (54.5)	17 (68.0)	
CEA			.763
<6	7 (31.8)	9 (36.0)	
≥6	15 (68.2)	16 (64.0)	
CA199			.522
<37	6 (27.3)	8 (32.0)	
≥37	16 (72.7)	17 (68.0)	

CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CR = complete remission, ECOG PS = Eastern Cooperative Oncology Group Performance Status, PR = partial remission, SD = stable disease.

Subgroup analyses were generally consistent with the primary finding. We can see a benefit of maintenance in all subgroups for PFS (Fig. 2A). However, subgroup analysis did not show major differences to OS (Fig. 2B). In a multivariate model on PFS, the following 2 subcategories differed significantly: treatment group and site of primary tumor (Table 2).

After progression of the disease, all patients in 2 groups received subsequent anti-cancer treatments (Table 3). There were 4 (16%) patients in metronomic capecitabine group and 3 (13.6%) patients in observation group received the FOLFIRI regimen, respectively. Four (16%) and 5 (22.7%) patients received the regimen of irinotecan and raltitrexed, respectively. The regimen including irinotecan and S1 was administered to 7 (28%) patients in the metronomic capecitabine and 6 (27.3) in the observation group. Ten (40%) patients in the metronomic capecitabine group and 8 (36.4%) patients in the metronomic capecitabine group received targeted therapy, including cetuximab or bevacizumab.

3.3. Safety

During the trial, treatment-related grade 3/4 AEs were reported in 8 (32.0%) patients in the capecitabine group and 4 (21.7%) patients in the observation group (Table 4). The most frequent AEs in the metronomic capecitabine group were neutropenia, diarrhea, hand-foot skin reactions, and mucositis. No toxicity-associated deaths occurred in this study. Most AEs were mild and manageable.

4. Discussion

Our study showed that maintenance treatment with metronomic capecitabine significantly improved median PFS compared with observation. The second endpoint, median OS, was months longer in maintenance group than in the observation group, but unfortunately this result did not reach statistical significance. Our results indicated that metronomic capecitabine is perhaps an optional maintenance therapy in patients with mCRC after first-line chemotherapy.

The prolonged chemotherapy in mCRC patients is often associated with cumulative toxicity, such as oxaliplatin-induced neuropathy and irinotecan-induced steatohepatitis. Therefore, seeking efficient and low toxic maintaining regimens without

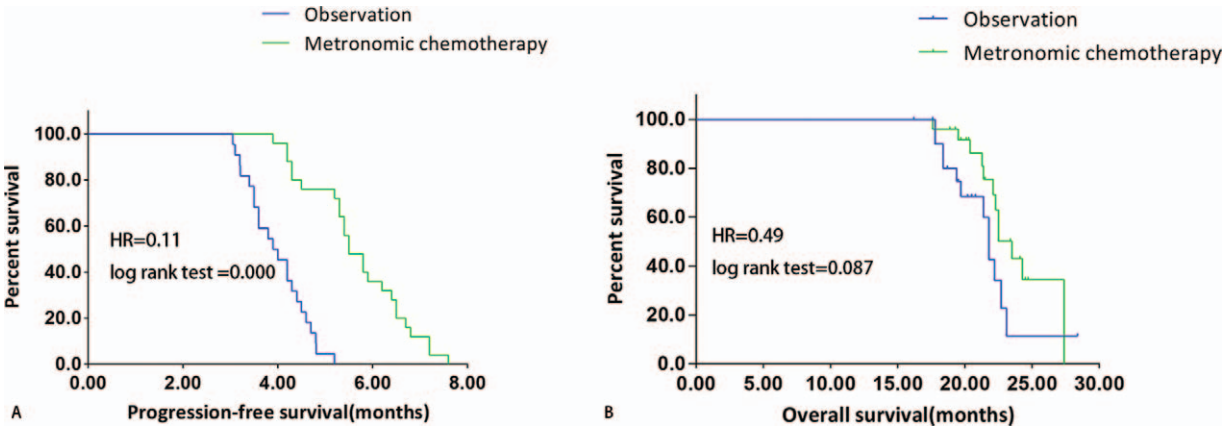

Figure 1. Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in 2 groups. HR = hazard ratio.

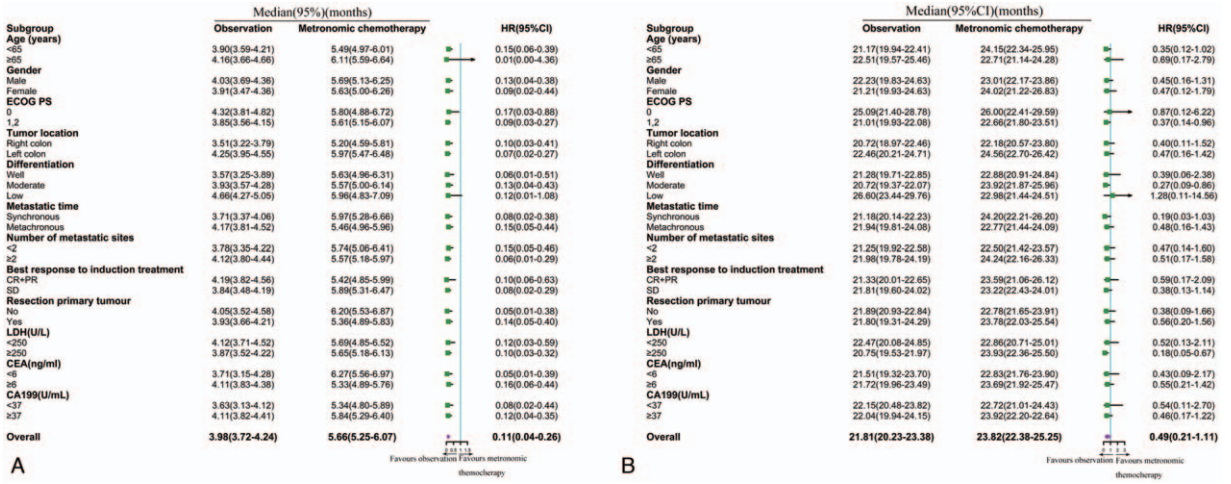

Figure 2. Subgroup analyses for progression-free survival (A) and overall survival (B) in 2 groups. CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, CR = complete remission, ECOG PS = Eastern Cooperative Oncology Group Performance Status, LDH = lactate dehydrogenase, PR = partial remission, SD = stable disease.

compromising survival is urgently needed in these patients. Some recent studies have investigated a variety of approaches in mCRC patients with the aim of reducing the treatment burden while maintaining a favorable outcome. The OPTIMOX trial[23] evaluating maintenance therapy with 5-FU/LV compared with continuous FOLFOX4 (OPTIMOX1) or total cessation of chemotherapy (OPTIMOX2) demonstrated that 5-FU-based maintenance therapy compared with complete chemotherapy discontinuation may be associated with inferior outcomes. The MACRO trial[24] suggested that maintenance therapy with bevacizumab might be an appropriate option following induction XELOX plus bevacizumab, with mild improvement in PFS. The CAIRO3 trial[25] showed a significant prolongation in PFS with an active maintenance treatment that included capecitabine plus bevacizumab after an initial XELOX plus bevacizumab compared with observation alone. Bevacizumab alone vs no treatment has also been investigated in the AIO 0207 trial[26] and in the PRODIGE 9[27] trial. Although the patients with bevacizumab maintenance showed prolonged PFS, the differences were not statistically significant in either study, which suggested that bevacizumab as a single drug has some activity, but less than in combination with fluoropyrimidine for PFS.

The European Society for Medical Oncology consensus guidelines recommend that a combination of fluoropyrimidine plus bevacizumab is an optional maintenance treatment following induction treatment with fluoropyrimidine, oxaliplatin, and bevacizumab.[28] However unregulated drug prices increase cancer therapy costs and yield an incremental economic burden. One study[29] investigated the cost effectiveness of capecitabine and bevacizumab maintenance treatment based on the CAIRO3 study results. Despite the fact that maintenance treatment improved health outcomes and prolonged PFS in mCRC, CAP-B maintenance may not be considered cost-effective. Another study[30] also indicated that antineoplastic therapy is expensive for payers and society. The price of capecitabine and bevacizumab maintenance therapy would need to be reduced by 93% to make it cost-effective. Recently, maintenance therapy with single agent of capecitabine can be considered an alternative option following first-line chemotherapy in mCRC patients with acceptable toxicities.[9] Due to the coverage of medical insurance, capecitabine did not add to the economic burden of patients and might be a cost-effective choice from the perspective of health economics.

Conventional anticancer chemotherapy uses molecules designed to interfere with the cell replication machinery to obtain a cytocidal or cytostatic effect on the rapidly dividing tumor cells. This can involve some serious side effects and lengthy drug-free breaks are thus required for recovery, particularly to overcome myelosuppression before starting subsequent cycles.

Table 2

Multi-factor analysis for progress-free survival.

	HR	95%CI	*P*
Age	1.064	0.454–2.498	.886
Gender	0.712	0.314–1.617	.417
ECOG PS	0.627	0.253–1.556	.314
Tumor location	0.272	0.115–0.645	.003
Differentiation	1.687	0.941–3.025	.079
Metastatic time	1.220	0.536–2.776	.635
Number of metastatic sites	0.363	0.126–1.041	.059
Response to induction treatment	0.625	0.273–1.431	.266
Resection primary tumor	1.699	0.705–4.098	.238
Serum lactate dehydrogenase	2.008	0.758–5.318	.161
CEA	1.659	0.503–5.472	.406
CA199	0.484	0.204–1.150	.100
Group	0.033	0.010–0.103	.000

CA199 = carbohydrate antigen 199, CEA = carcinoembryonic antigen, ECOG PS = Eastern Cooperative Oncology Group Performance Status.

Table 3

Treatments after disease progression.

Regime	Metronomic capecitabine (n,%)	Observation (n, %)
FOLFIRI	4 (16%)	3 (13.6)
Irinotecan + Raltitrexed	4 (16%)	5 (22.7)
Irinotecan + S1	7 (28)	6 (27.3)
Cetuximab + Chemotherapy	2 (8)	1 (4.5)
Bevacizumab + Chemotherapy	8 (32)	7 (31.9)

Table 4

Grade 3 to 4 adverse events considered relevant to treatment.

Events	Metronomic capecitabine (n, %)	Observation (n, %)
Hematologic		
Neutropenia	2 (8%)	1 (4%)
Anemia	1 (4%)	1 (4%)
Thrombocytopenia	1 (4%)	1 (4%)
Non hematologic		
Diarrhea	1 (4%)	1 (4%)
Hand-foot skin reaction	2 (8%)	1 (4%)
Mucositis	1 (4%)	

During these interruptions in treatment, recolonization of the tumor cells with chemo-resistant clones ultimately leads to treatment failure.[31] The metronomic schedule, traditionally defined as the frequent administration of chemotherapeutic agents at doses significantly below the MTD, with no prolonged drug-free breaks, represents a paradigm shift in cancer treatment. The reduction in drug-related toxicity constitutes an improvement in quality of life and allows chemotherapy to be extended to patients unfit for traditional treatments. The results from the MOMA trial indicated that the addition of metronomic chemotherapy to maintenance with bevacizumab does not significantly improve the PFS of mCRC patients.[19] However, there are 3 differences compared to our study. Firstly, in this study, patients were randomized at the beginning instead of at the end of the induction treatment. Secondly, 28% of enrolled patients never received maintenance, thus reducing the power to detect a difference in PFS. Thirdly, a lack of balance in response to induction chemotherapy between the 2 groups actually exposed to maintenance may have occurred. In fact, there is some evidence evaluating the efficacy of metronomic chemotherapy in various cancers, including breast cancer,[15] hepatocellular carcinoma,[18] prostate cancer,[32] squamous cell carcinoma of head and neck,[33] etc. The results of our study also suggested that metronomic capecitabine as a maintenance treatment, may be prolong the PFS of patients with mCRC compared to observation. These data provided some evidence for metronomic capecitabine as a maintenance treatment following the induction regimen of XELOX, though further research is warranted.

Although our data showed that median PFS was extended significantly in the group of maintenance treatment with metronomic capecitabine compared with observation, our study had some shortcomings as follows. Firstly, this study was small in scale. Of course, this may have something to do with the time span of the program and China's health care policy. Secondly, above 50% of patients in 2 groups are alive by now, so median OS is not accurate. Thirdly, this study did not compare the quality of life or the cost-effectiveness between 2 groups. There was also no statistically significant difference in median OS, we thought there were 3 reasons for the present results. Firstly, the number of patient enrollment was limited, these results from this study needed further research to be verified. Secondly, the frequent treatment choices maybe influenced the results. As bevacizumab, cetuximab and regorafenib entered the medical insurance successively, these events maybe affect treatment options and patient's OS time. Thirdly, in our country, genetic tests are very expensive for most patients and charged item is not covered by health insurance, so gene difference expression is maybe a distorted factor. However, our study provided an exploratory choice for patients with mCRC who have completed all induction chemotherapy with XELOX. Another study[9] assessed role of single-agent capecitabine as maintenance therapy in patients with mCRC (1000 mg/m^2 2 weeks on and 1 week off). If 1 patient received 1 cycle capecitabine maintenance, the amount of drug used is 84 pills and it is 42 pills if metronomic capecitabine chemotherapy was administrated. According to the study, each patient received an average of 6 months of maintenance chemotherapy. If a piece of capecitabine is 27.5 yuan, the patient will need to spend 13860 yuan in 6 months. Using the same algorithm, in our study 1 patient spent 6600 yuan for half a year. Only this item can save 7260 yuan for each patient every 6 months. In addition, compared with our treatment regimen, capecitabine maintenance chemotherapy causes more grade 3/4 adverse reactions (41.9% vs 32.0%). The subsequent symptomatic treatment may cause more medical costs. Overall, compared with capecitabine maintenance chemotherapy, metronomic chemotherapy is more cost-effective when the survival benefits are similar. Metronomic capecitabine maintenance treatment did not add additional burden and inconvenience for patients because this medicine is cheaper and can be obtained in outpatient settings. This offers a choice of maintenance treatment to patients with lower incomes or with mobility difficulties.

5. Conclusion

Maintenance treatment with metronomic capecitabine was superior to observation in term of disease-free survival following first-line chemotherapy of XELOX in patients with mCRC with controlled toxicities. However, there was no statistically significant difference in median OS between 2 groups.

Author contributions

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