

Efficacy and safety of metronomic chemotherapy in maintenance therapy for metastatic colorectal cancer

A systematic review of randomized controlled trials

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Abstract

Background: The current studies on metronomic chemotherapy in mCRC are all aimed at patients after multi-line therapy failure, and only a few studies have focused on maintenance treatment after successful first-line therapy.

Methods: The PubMed, Embase, Cochrane Library, Wanfang, CNKI, and VIP were searched, and the relevant data was extracted, including media progression-free survival (mPFS), media overall survival (mOS), and grade 3/4 adverse events (AEs).

Results: We included 4 randomized controlled trials (RCTs), 2 RCTs showed that metronomic maintenance chemotherapy could significantly improve mPFS compared to observation group; another RCT showed that metronomic maintenance chemotherapy group did not have low mPFS than the bevacizumab maintenance treatment (MT). The final RCT showed that dual-agent metronomic chemotherapy combined with bevacizumab MT did not improve mPFS compared with bevacizumab MT. The 3 RCTs showed that the metronomic maintenance therapy could not effectively improve mOS in mCRC compared to observation group or bevacizumab MT, while another RCT reported that the mOS in metronomic maintenance chemotherapy group was similar to bevacizumab MT. AEs was mostly mild and manageable. Grade ≥ 3 AEs are mostly nonhematological toxicity, and no deaths related to AEs were reported.

Conclusion: This systematic review indicates that metronomic chemotherapy for mCRC MT can improve mPFS in some patients and is relatively safe. However, improvements in OS in most RCTs are arguable. Therefore, we need further studies to verify its long-term efficacy.

Abbreviations: AEs = adverse events, HFS = hand-foot syndrome, MC = metronomic chemotherapy, mCRC = metastatic colorectal cancer, mOS = media overall survival, mPFS = media progression-free survival, MT = maintenance treatment, RCT = randomized controlled trials.

Keywords: efficacy, maintenance therapy, metastatic colorectal cancer, metronomic chemotherapy, safety

1. Introduction

According to the Global Cancer Statistics Report (2020), there were 935,173 deaths from colorectal cancer worldwide, accounting for 9.4% of all cancer deaths, and the mortality rate ranking second in the world.^[1] From 2000 to 2018, due to a change in diet and lifestyle, the incidence of colorectal cancer among adults (aged 50 and over) rose from 20% to 61%.^[2] As the early symptoms of colorectal cancer are not obvious,

most patients are diagnosed in the advanced stage (they lose the chance of surgical intervention), and the 5-year survival rate is only 14%.^[2] Currently, the treatment of metastatic colorectal cancer (mCRC) is mainly through cytotoxic drugs (such as oxaliplatin, capecitabine, and irinotecan) or combined targeted therapy with monoclonal antibodies (such as bevacizumab and cetuximab). The induction therapy prolongs life, and a small number of patients with microsatellite instability-high (MSI-H) can benefit from immune checkpoint inhibitors. Induction

LC and XC contributed equally to this work.

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chemotherapy kills tumor cells when the maximum tolerated dose of the drugs is used (a high-intensity antitumor therapy), but the real challenge is to find ways to consolidate this curative effect. Should one choose to continue induction therapy with the original regimen, maintenance treatment (MT) with standard doses of some drugs, or simply conduct regular observations? If the original regimen is continued, the adverse drug reactions caused by a long-term treatment, such as cumulative use of oxaliplatin > 1000 mg/m², will increase the risk of peripheral neurotoxicity in patients.^[3] In 2020, Sonbol and coworkers performed a network META-analysis of randomized controlled trials (RCT) of diverse MT strategies in patients with mCRC. They showed that only after 16 weeks of first-line induction of FPOX or FPIRI, subsequent treatment strategies could be applied. Compared with the standard-dose fluorouracil ± bevacizumab MT group and the observation group, patients cannot be maintained from the original induction regimen until disease progression. Also, the comparison of the effectiveness between the standard dose fluorouracil ± bevacizumab MT group and the observation group showed that although the former can significantly improve progression-free survival, OS was not statistically difference.^[4] In this regard, it is necessary to explore a new MT strategy for these patients. At present, other MT strategies for mCRC are still being explored, such as the use of EGFR inhibitors, but no optimal MT for mCRC is reported.^[5] To achieve the purpose of prolonging the life of patients, MT also needs to take into account the potential adverse reactions caused by drugs and their impact on the quality of life of the patients. Can metronomic chemotherapy (MC) be used for the MT of mCRC? As early as 2000, some studies proposed MC for the treatment of advanced malignant tumors, and it has been found effective in tumors of different origins, including breast cancer, lung cancer, and ovarian cancer.^[6–9] MC can achieve the purpose of anti-tumor by using continuous administration of drugs at low doses. This can also reduce the incidence and severity of adverse drug reactions and prevent drug resistance. Therefore, MC may bring new hope to patients who need MT to provide anti-tumor efficacy even after the first-line therapy is over. However, the current studies on MC in mCRC are all aimed at patients after multi-line therapy failure, and only a few studies have focused on MT after successful first-line therapy. Therefore, the purpose of this study is to assess the efficacy and safety of MC in mCRC patients and to provide appropriate medication references for patients whose disease is in remission or under stable conditions after first-line induction therapy and in need of MT.

2. Methods

2.1. Study selection

The databases of scientific literature, including PubMed, Embase, Cochrane library, China Wanfang, China CNKI, and China VIP, were searched for relevant articles published as of February 28, 2022. The free words and subject headings search method was used. The following keywords were used for the search: “Colorectal Neoplasms” or “Colorectal Tumors” or “Colorectal Carcinoma” and “maintenance treatment” or “metronomic.”

2.2. Inclusion criteria

The inclusion criteria were as follows: RCTs of MC for mCRC; Eastern Cooperative Oncology Group performance status (PS) ≤ 2 points; received at least 16 to 24 weeks of first-line induction chemotherapy, and the efficacy assessment was response or stable disease; The treatment group received single-drug or dual-drug MC ± targeted drug MT, while the control group received observation or targeted drug MT; adequate hematologic, hepatic and renal function.

2.3. Exclusion criteria

The exclusion criteria were as follows: Multiple lines of chemotherapy; severe toxicity caused by induction chemotherapy; cardiovascular disease poorly controlled by medication; a history of neurological or psychiatric disorders.

2.4. Data extraction

Our teams formulated the search method. Two reviewers checked the articles separately, shortlisted relevant literature, and extracted information. Arguments were solved after discussion with our team. The first author, the year of publication, country, sample size, media progression-free survival (mPFS), media overall survival (mOS), and grade 3/4 adverse events (AEs) were extracted.

2.5. Quality evaluation

Two reviewers independently performed the quality evaluation of the scientific articles included in this study. Modified Jadad score was a tool to assess the quality of RCT. Then, the risk of bias for each article was assessed by RevMan software (version 5.4). Disagreements on the quality evaluation process were solved after discussion with our team till a consensus was reached.

2.6. Pooled data analysis

A qualitative synthesis of the eligible studies was conducted in the form of a table showing the research characteristics, clinical characteristics, and reported efficacy and safety values. Meta-analysis was not performed because data on relevant outcomes were insufficient for quantitative synthesis and the tabulated results indicated high methodological heterogeneity between the studies.

3. Results

3.1. Eligible studies

The literature screening process was conducted as recommended by the PRISMA statement. 877 articles were retrieved from the databases search, including 139 from PubMed, 771 from Cochrane Library, 6 from Embase, 14 from CNKI, 31 from China Wanfang, and 16 from China VIP. We excluded 780 articles because of the following reasons: duplicate papers, reviews, irrelevant topics, retrospective studies, and studies reporting in vitro test results. After a full-text review, 8 articles were selected, and 4 were excluded. Among the selected articles, 1 article could not be extracted, 1 lacked outcome indicators, 1 was a single-arm trial, and 1 was non-MC. The remaining 4 papers were eligible.^[10–13] Flow chart is shown in Fig. 1.

3.2. Quality evaluation

The quality of the RCTs were assessed by modified Jadad score. The scoring system includes 4 items — random sequence, allocation concealment, blinding, withdrawal, and failure in follow-up. The score value of 1–3 was considered low-quality literature, and 4–7 were of high quality. However, allocation concealment and blinding were not used in some of these studies. The results showed that 2 of the articles are 5 points, and the other 2 are 3 points. And the results of articles bias risk showed that there were 2 articles with low risk of bias, and 2 articles with unclear risk of bias, as shown in Fig. 2.

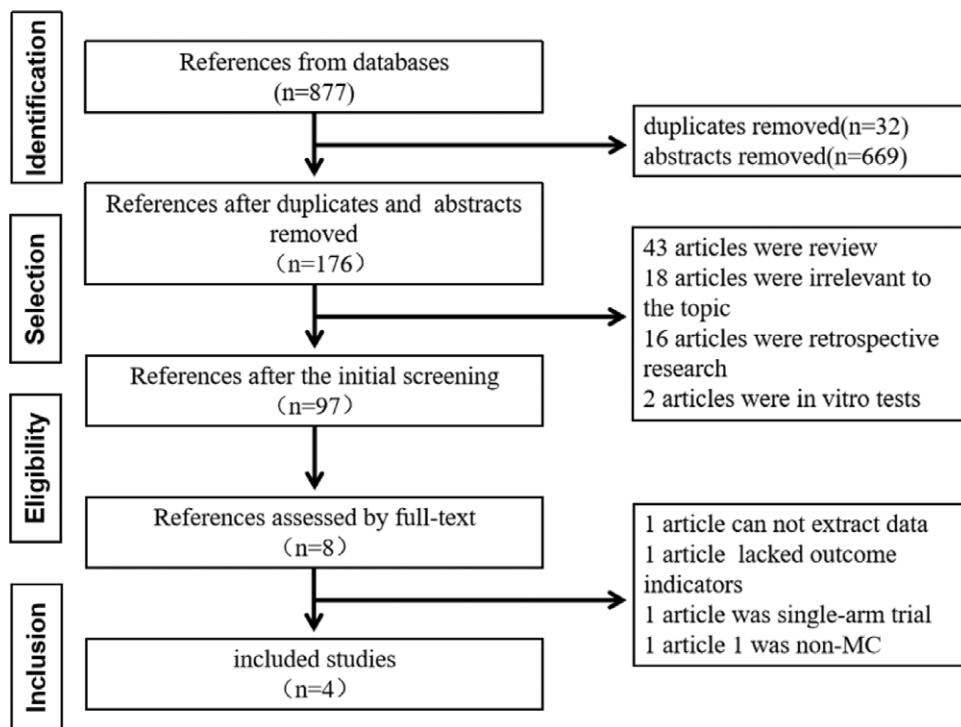


Figure 1. Flowchart of the article retrieval and selection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cremolini C 2019	+	+	-	-	+	+	?
Geng R 2020	?	?	-	-	+	+	?
Hagman H 2015	?	?	-	-	+	+	?
Simkens LH 2015	+	+	-	-	+	+	?

Figure 2. Risk of bias appraisal for each literature.

3.3. Characteristics of the included studies

The basic characteristics are shown in Table 1. In total, 836 patients were included in the 4 RCTs,^[10-13] 1 each from China,

Italy, Switzerland, and New Zealand. All 836 patients were split into 2 groups. The treatment group received single-agent or double-agent MC ± bevacizumab (2 studies used capecitabine; one study used capecitabine + bevacizumab, and another study involved capecitabine + cyclophosphamide + bevacizumab). The control group was either on placebo or treated with only bevacizumab as MT. Thus, 413 patients were treated with MC, and 423 were either observed or given bevacizumab monotherapy MT.

3.4. The effectiveness of MC in mCRC MT

All 4 selected studies included RCTs and had reported on the mPFS and mOS of the participants. Geng et al included 48 patients who received capecitabine MC for maintenance or observation after completing 18 weeks of XELOX induction chemotherapy as a first line of treatment. After 22 months of follow-up, they found that the mPFS of the patients in the 2 groups had significantly improved by 5.66 months (95%CI: 5.25–6.07) in capecitabine MC group and 3.98 months (95%CI: 3.71–4.24) in observation group (HR 0.11 95%CI: 0.04–0.26, P = .000). The capecitabine MC group showed a slight improvement in mOS when compared to observation group, even though an appreciable statistical difference in the mOS was absent. The mOS was 23.82 months (95%CI: 22.38–25.25) in capecitabine MC group and 21.81 months (95%CI: 20.23–23.38) in observation group (HR 0.49 95%CI: 0.21–1.11, P = .087).^[10] Hagman et al conducted the first RCT with capecitabine MC maintenance versus bevacizumab maintenance in 67 patients with stable disease after 18 weeks of XELOX/FOLFOX/FOLFIRI/XELIRI induction chemotherapy; follow-up was done till 34.5 months. The statistics displayed that mPFS and mOS of capecitabine MC group were not inferior to those of the bevacizumab MT, with mPFS of 3.7 and 3.9 months and mOS of 28 and 26.4 months, respectively. However, the mPFS and mOS results between the 2 groups were not statistically analyzed.^[11] Simkens et al divided 557 patients into treatment and observation groups. Both groups received 6 cycles of induction chemotherapy (capecitabine + oxaliplatin + bevacizumab), and then only the treatment group received

Table 1
Basic information and specific characteristics of the eligible clinical trials.

Author	Year	Country	Trial design	Induction regimen	Median follow up (months)	Patients			Age		Schedule	
						Total	T	C	T	C	T	C
Geng R	2020	China	NA RCT	XELOX	22.0	47	25	22	-	-	Cap (500mg bid continuously)	Ob
Cremolini C	2019	Italy	II RCT	FOLFOXIRI + Bev	47.8	165	77	88	62 (31–74)	61 (23–74)	CTX + Cap + Bev (cap 500mg tid + CTX-50mg + Bev-7.5mg/kg,q3w)	Bev (7.5mg/kg,q3w)
Hagman H	2015	Sweden	III RCT	XELOX, FOLF- OX, FOLF- IRI, XELIRI	34.5	67	33	34	63 (45–79)	65 (44–75)	Cap (500mg bid continuously)	Bev (7.5mg/kg,q3w)
Simkens LH	2015	Netherlands	III RCT	Capox-B	48.0	557	278	279	63 (26–81)	64 (31–81)	Cap + Bev (cap 625mg bid continuously + bev-7.5mg/kg,q3w)	Ob

Bev = bevacizumab, C = control group, Cap = capecitabine, CTX = cyclophosphamide, T = treatment group.

the MT with capecitabine MC + bevacizumab. After 48 months of follow-up, they found that mPFS in capecitabine MC group was 8.5 months (95%CI: 6.5–10.3) and in observation group was 4.1 months (95%CI:3.9–4.2); capecitabine MC group had no significant effect on patients' quality of life. The mOS of the capecitabine MC group and the observation group was 21.6 months (95% CI 19.3–23.8) and 18.1 months (95% CI 16.3–20.2). Although the mOS of MC group was better than observation group, there was no significant statistical difference.^[12] In another phase III RCT, Cremolini et al administered capecitabine + cyclophosphamide MC + bevacizumab maintenance or bevacizumab monotherapy MT to 165 patients after 8 cycles of induction therapy with FOLFOXIRI + bevacizumab. A follow-up after 47.8 months showed mPFS of 10.3 months and 9.4 months (HR 0.94 95%CI:0.82–1.09, $P = .680$) and mOS of 22.5 months and 28 months (HR 1.16 95%CI: 0.99–1.37, $P = .336$) in capecitabine + cyclophosphamide MC + bevacizumab maintenance and observation groups. However, the data was statistically insignificant. The results suggest that double-agent MC + bevacizumab MT did not significantly improve PFS or OS in mCRC.^[13]

3.5. The safety of metronomic maintenance chemotherapy in mCRC

All the 4 eligible studies reported adverse reactions of grade ≥ 3 with an incidence rate of 36.36% (304/836), which were then classified as hematological toxicity and non-hematological toxicity. The incidence of hematological toxicity was 3.29% (10/304), mainly due to neutropenia. The incidence of non-hematological toxicity was 96.71% (294/304) which manifested as hand-foot syndrome (HFS), mucosal inflammation, and diarrhea.

3.6. Subgroup analysis

3.6.1. Based on genotypes. This subgroup analysis was conducted in 3 of the 4 RCTs discussed in this review. Cremolini and coworkers had conducted a subgroup analysis based on the mutations found in RAS/BRAF (oncogenes implicated in colorectal cancer). They showed that although the mOS of patients, with no mutations in RAS/BRAF, was 31.3 months (95% CI: 15.6–45.8), that of the RAS mutant group was 24.9

months (95%CI: 12.4–45.3) (HR 1.20 95%CI: 0.77–1.87, $P = .414$), and BRAF mutation group was 19.2 months (95%CI: 11.5–35.2) (HR 1.52 95%CI: 0.79–2.89, $P = .208$). The data was statistically insignificant, suggesting that the OS of patients was not affected by gene mutations in RAS/BRAF.^[13] Hagman et al also conducted a subgroup analysis based on various mutations in the KRAS gene. They showed that the mPFS and mOS of patients with KRAS mutation (treated with capecitabine MC) were not inferior to patients receiving bevacizumab MT. A mPFS of 3.7 months and 3.9 months (HR 1.19 95%CI: 0.72–1.97, $P = .501$) and mOS of 28 and 26.4 months (HR 1.57, 95%CI: 0.87–2.84, $P = .128$) were reported in capecitabine MC and bevacizumab MT, respectively.^[11] Goey et al conducted a post hoc subgroup analysis of the CAIRO3 study conducted by Simkens et al. The grouping factors were RAS/BRAF gene mutations and mismatch repair. The analysis found that—for mCRC patients receiving capecitabine MC + bevacizumab MT, except for the OS of the RAS mutation subgroup, patients could not benefit from MT. However, the PFS and OS of other subgroups could benefit. The mPFS of RAS/BRAF wild-type (treated with capecitabine MC + bevacizumab group and observation group) were 8.2 and 5.8 months (HR 0.36 95%CI: 0.25–0.54, $P < .0001$), mOS was 25.7 months and 19 months (HR 0.68 95%CI: 0.46–1.00, $P = .047$). The mPFS of patients with BRAF (V600E) mutation (treated with capecitabine MC + bevacizumab and observation group) were 9.5 months and 2 months (HR 0.19 95%CI: 0.08–0.44, $P < .0001$), mOS was 15.8 months and 13.6 months (HR 0.32 95%CI: 0.14–0.73, $P = .007$), respectively.^[12,14]

3.6.2. Based on the location of the primary tumor. Two of the 4 eligible RCT studies had performed subgroup analysis. Cremolini et al used the location of the primary tumor (left colon or right colon) as a grouping factor, and the subgroup showed that the primary tumor location had no significant effect on patient mOS. It was 25.4 months (95%CI: 13.7–43.1) for tumors originating in left hemicolon and 23 months (95%CI: 12.5–45.3) for the right hemicolon (HR 0.90 95%CI: 0.66–1.24, $P = .522$).^[13] Goey et al performed a post hoc analysis of the CAIRO3 trial conducted by Simkens et al. This analysis also used primary tumor location as a grouping factor to explore its impact on patient survival, and the results showed that patients with right colon could benefit from capecitabine MC. However, in patients with primary tumors at left hemicolon, capecitabine MC treatment had improved mPFS but not the OS.^[12,14]

Evaluation index				Grade3/4 Aes				AE		
T		C		T	C			evaluation criteria	Quality of Jadad evidence score	
mPFS (months)	OS (months)	mPFS (months)	mOS (months)	Hematologic	Nonhematologic	Hematologic	Nonhematologic			
5.66 (95%CI 5.25–6.07)	23.82 (95%CI 22.38–25.25)	3.98 (95%CI 3.71–4.24)	21.81 (95%CI 20.23–23.38)	4	4	3	2	CTCAE v3.0	High	5
10.3 (70%CI:9.1–11.6)	22.5 (95%CI:18.4–25.8)	9.4 (70%CI:8.3–10.6)	28.0 (95%CI:20.0–33.6)	3	10	0	4	CTCAE v4.0	Low	3
3.7	28	3.9	26.4	0	5	0	7	CTCAE v3.0	Low	3
8.5 (95% CI 6.5–10.3)	21.6 (19.3–23.8)	4.1 (95% CI 3.9–4.2)	18.1 (95% CI 16.3–20.2)	0	95	0	167	CTCAE v3.0	High	5

4. Discussion

We included 4 articles, all of which were RCTs, and their conclusions varied on whether metronomic MT of mCRC patients could improve their mPFS and mOS. In terms of mPFS, 2 RCTs studies showed that metronomic maintenance chemotherapy could significantly improve mPFS in patients compared to the observation group; another RCT showed that the metronomic maintenance chemotherapy group did not have low mPFS than the bevacizumab MT group. The final RCT study on mCRC patients, treated with induction chemotherapy (FOLFOXIRI), showed that dual-agent MC combined with bevacizumab MT did not improve mPFS in patients compared with bevacizumab MT. In terms of mOS: the 3 RCTs studies showed that the metronomic maintenance therapy could not effectively improve mOS in mCRC patients compared to the observation group or bevacizumab MT, while another RCT reported that the mOS in the metronomic maintenance chemotherapy group was similar to the bevacizumab maintenance group. In all the 4 RCTs included here, AEs in patients was mostly mild and manageable. Grade ≥ 3 AEs are mostly non-hematological toxicity, and no deaths related to AEs were reported.

The drugs currently used for MC of mCRC mainly include fluorouracils (FU), camptothecins, and cyclophosphamide.^[15–17] Three of the 4 included RCT studies included capecitabine in the MT, and the fourth RCT was on capecitabine + cyclophosphamide dual-drug MC. Capecitabine is a prodrug of 5-FU, which is initially converted into 5'-deoxyfluridine by carboxylesterase and cytidine deaminase in vivo, then transformed into 5-deoxy fluoruridine by cytidine phosphorylase, and finally converted into active 5-FU. This design can greatly reduce the expression of fluorouracils in the gut and bone marrow, thereby reducing adverse drug reactions.^[18] Studies have shown that mCRC patients who require salvage therapy can benefit from capecitabine MC. One study^[19] included 68 patients with mCRC who were unable to receive standard chemotherapy due to adverse drug reactions or failure of chemotherapy at one or more metastatic sites. A single-arm study, with a 6.5-month follow-up, of low-dose capecitabine (1500 mg daily) in patients showed that capecitabine MC had moderate activity and was well-tolerated in mCRC who had received multiple lines of chemotherapy or were frail. In recent years, studies have shown that cyclophosphamide MC can inhibit the growth of tumor blood vessels not only to achieve the anti-tumor efficacy but to enhance

the immune response as well.^[20–22] To verify the effectiveness of cyclophosphamide MC in enhancing the immune response generated by MVA-5T4 vaccination, Scurr et al divided 52 patients, with stable and inoperable mCRC after induction chemotherapy, into 4 groups — cyclophosphamide MC group (50 mg/bid, d1–7, d15–21), MVA-5T4 treatment group, cyclophosphamide MC + MVA-5T4 group, and the observation group. The results showed that cyclophosphamide MC can reduce Foxp3⁺ Tregs (T regulatory cells) and prolong PFS. Also, the patients did not experience any grade ≥ 3 AEs. Although low-dose cyclophosphamide did not increase the immune activity of the MVA-5T4 vaccine, it induced a beneficial immune response, prolonged survival, and showed better tumor efficacy.^[17]

Current MT for mCRC patients is mostly based on standard-dose chemotherapeutics, which is different from our studies based on MC. Luo et al studied the efficacy and safety of capecitabine monotherapy MT in mCRC patients who received 18 to 24 weeks of XELOX regimen after induction chemotherapy. The study randomly assigned patients to the capecitabine standard-dose maintenance group (capecitabine 1000 mg/m², d1 to 14, twice a day, then stopped for one week for every 3 weeks of drugs; continued this cycle) and the observation group. After 29 months of follow-up, although the mPFS of the capecitabine group was significantly improved compared to the observation group, the improvement in OS was insignificant. In terms of safety, compared with the observation group, the incidence of grade 3/4 AEs in the capecitabine group was 41.9%, which was significantly higher than that in the observation group (22.4%). Among all the AEs, the most common were neutropenia in 12.5% of patients (17/136), HFS in 5.9% (8/136), and mucositis in 5.9% (8/136). Throughout the trial, 8.8% (12/136) of patients in the capecitabine group had dose reductions due to HFS (50%) and diarrhea (25%). Thus, mCRC patients had tolerable adverse reactions, and capecitabine standard-dose maintenance may be considered an appropriate choice after induction chemotherapy with XELOX or FOLFOX.^[23] In the 4 included RCTs, 2 RCTs used capecitabine 500 mg/bid metronomic maintenance therapy, 1 used capecitabine 500 mg/tid + cyclophosphamide 50 mg/d double-agent metronomic maintenance therapy, and the last one used capecitabine 625 mg/bid metronomic maintenance therapy continuously. The incidence of grade 3/4 AEs in the capecitabine 500 mg/bid group was less than 35%. Geng and coworkers showed that the incidence of HFS \geq grade 3 was 8% (2/25).^[10] In the study by Hagman et al, grade ≥ 3 HFS was

not reported.^[11] Capecitabine 500 mg/tid + cyclophosphamide 50 mg/qd double-agent group had a rate of \geq grade 3 AEs in 16.9%, of which the incidence of the HFS was 9.1% (7/77).^[13] Capecitabine 625 mg/bid group had a higher incidence of grade 3 AEs of about 60% (167/278), but no grade 4 AEs occurred. It may be due to the slightly higher incidence of AEs due to the combinatorial effect of bevacizumab. The common grade 3 AEs in the capecitabine 625 mg/bid group were hypertension in 24% (68/278), the HFS in 23% (64/278), and peripheral neuropathy in 10% (27/278).^[12] A total of 27 patients in the capecitabine 625 mg/bid group stopped treatment due to drug-related AEs. Although the incidence of the HFS was higher than that in the observation group, it did not affect the quality of life of patients. It can be seen that with respect to the incidence of \geq grade 3 AEs, capecitabine 500 mg/tid + cyclophosphamide 50 mg/qd double-agent group has a low incidence of grade \geq 3 AEs, capecitabine 500 mg/bid group had a slightly higher incidence, but the highest was observed in capecitabine 625 mg/bid group. Generally, the incidence of grade 3/4 AEs in metronomic maintenance therapy was lower than that in capecitabine standard dose MT, and the incidence of grade 3/4 AEs in HFS was lower. There are few reports of drug discontinuation due to AEs in metronomic maintenance therapy.

Economically, the cost of MT for patients with standard-dose chemotherapy is usually higher than that of MC. As early as 2005, Bocci et al conducted a pharmaceutical economics evaluation of cyclophosphamide/methotrexate MC in patients with metastatic breast cancer (under palliative care) and showed that it was significantly different from 11 single-agent or combination chemotherapy (e.g., vinorelbine, docetaxel, gemcitabine, paclitaxel, and docetaxel + carboplatin). The low-dose cyclophosphamide/methotrexate has been evaluated as a cost-effective/cost-saving option for metastatic breast cancer patients under palliative care.^[24] There is no economic analysis of capecitabine MC, capecitabine standard doses, and other maintenance regimens, but hopefully, this will be addressed in future studies.

Studies have found that the prognosis of mCRC is related to the location of the primary tumor and the gene mutations in KRAS, RAS, and MSS. The prognosis when the tumor originates in the left colon is better than that of the right colon.^[25] Then the origin of the primary tumor and the status of KRAS, RAS, and MSS may also have a certain impact on the benefit of metronomic maintenance therapy. In this systematic review, 3 RCTs have conducted genetic assessments of patients and associated it with the effectiveness of MC. Among them, 1 study only considered KRAS mutations in mCRC patients. The results indicated that in patients with KRAS mutations, the mPFS and mOS of capecitabine MC were similar to bevacizumab MT. Two RCTs have investigated whether the origin of the primary tumor can benefit from metronomic maintenance therapy, but the included studies had small sample sizes to conclude about the benefits of metronomic maintenance therapy being associated with the primary tumor location. However, the induction chemotherapy regimens used in mCRC patients in the included studies were different (included XELOX, FOLFOX + bevacizumab, CAPEOX + bevacizumab, XELOX/FOLFOX/XELIRI/FOLFIRI + bevacizumab). Hence, the question arises of whether different induction chemotherapy regimens and induction chemotherapy, with or without bevacizumab, affect the efficacy and safety of metronomic maintenance therapy? Also, how to determine the dose and schedule of MC after first-line induction chemotherapy? These questions will probably be answered in future research.

There are some limitations to this systematic review. Firstly, there are inconsistencies in the experimental group and the observation group in the eligible RCT studies, which may have influenced the conclusion and application of the study. Therefore, the results of this study should be comprehensively considered in combination with the actual situation of patients when applied in clinical practice. Secondly, the number of

studies included here is very small (only 4 RCTs are included), which may affect the reliability of the results and the extrapolation of the conclusions. Thirdly, the included RCTs were not blinded, and only 2 used randomized control for allocation concealment; the remaining 2 were not subject to allocation concealment, which may affect the credibility of the study, resulting in a lower quality of the included studies. Finally, 2 RCTs in the included studies were sponsored by pharmaceutical companies, and in one of the studies, the sponsor participated in the trial design. Although the sponsor did not participate in the specific implementation of the specific trial, it may have a certain impact on the trial results. This systematic review suggests that further clinical research should pay attention to adopting sufficient randomization methods, allocation scheme concealment, and blinding methods in research design and methods to reduce various biases such as selectivity, implementation, measurement, and attrition. Research results should provide detailed and fully transparent research information for readers to judge the authenticity of the research results.

5. Conclusion

This systematic review indicates that MC for mCRC MT can improve mPFS in some patients and is relatively safe. Most of the adverse reactions were mild and manageable, and no AE-associated deaths were reported. However, improvements in OS in most RCTs are arguable. Therefore, we need further studies to verify its long-term efficacy.

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Author contributions

Conceptualization: L.C., X.C. and C.M.L.

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