Efficacy and Safety of Capecitabine Metronomic Chemotherapy versus Conventional Chemotherapy as Maintenance Strategy in Responders After Induction Therapy in Metastatic Colorectal Cancer

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Study protocol

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Abstract

Background: The aim of this study is to demonstrate that capecitabine metronomic chemotherapy is non-inferior to capecitabine conventional chemotherapy as maintenance treatment, who have responded to 16-18 weeks first-line chemotherapy in metastatic colorectal cancer (mCRC).

Methods: The study design is a prospective, randomized, open label, phase II clinical trial. Those mCRC patients who respond well after 16-18 weeks of standard doublet chemotherapy as induction may enrolled into this study, randomly divided into capecitabine metronomic group or standard dosage group. The duration of disease control after randomization and progression free survival from enrollment are primary endpoints. Meanwhile, the overall survival, safety and quality of life are secondary endpoints. The sample size required to achieve the research objectives of this project is 79 cases in each group. The study recently started on 29-01-2018, and will last for 36 months.

Discussion: This project intends to study the efficacy and safety of capecitabine metronomic chemotherapy in the maintenance treatment of advanced colorectal cancer, and to explore the strategy of "low toxicity, high efficiency, economy and individualization" which is suitable for China's national conditions and pharmacoeconomics. It has great clinical application prospects and clear socio-economic value.

Background

Global Cancer Statistics 2018 indicated that there would be an estimated 18.1 million newly diagnosed cancer cases and 9.6 million cancer-related deaths in 2018. Among them, over 1.8 million new colorectal cancer cases and 881000 deaths were estimated to occur in 2018. Overall, colorectal cancer ranked third in all cancer incidence (6.1%) and second for mortality (9.2%)[1]. The incidence rates of colorectal cancer are about 3-fold higher in transitioned versus transitioning countries[1]. The difference may due to dietary patterns, obesity, and lifestyle factors. Standard screening and early detection programs have been conducted in the United States and Japan since 1990s[2], and the 5-year survival rate of colorectal cancer was increased from 51% (1990) to 65% (2012) while more and more patients were diagnosed as early staging[3]. Even so, there will be almost half of the colorectal cancer patients eventually develop metastasis and lose the chance to eradicate cancer[4]. For these patients, how to prolong the survival time and inhibit the growth of tumors on the premise of guaranteeing the quality of life, and transform the metastatic colorectal cancer (mCRC) into chronic diseases like diabetes and hypertension through long-term, low toxicity and effective drug treatment are of great clinical research value.

Drug therapies for mCRC patients were ranged from 5-fluorouracil monotherapy in the 1960s to 5-fluorouracil in combination with oxaliplatin or irinotecan and with or without targeted agents such as bevacizumab, cetuximab or panitumumab in the past decade. The median overall survival (OS) of mCRC patients was from less than 12 months to more than 33 months[5-11]. However, conventional chemotherapy usually gives the maximum tolerable dose of the drug, and will cause huge toxicity and

side effects while killing cancer cells. Chemotherapy-related vomiting, diarrhea, agranulocytosis, peripheral neurotoxicity and other serious adverse reactions occur as high as 5-20%[7, 12-14]. It takes a period of time for the body to recover from toxic and side effects after each routine chemotherapy administration, and repeated multiple cycles of administration are more likely to cause toxicity accumulation, which limits the number of courses of treatment. More importantly, after a period of high-intensity chemotherapy, how to continue to effectively and persistently inhibit the progress of cancer, while ensuring patients with good tolerance and quality of life, has been a hot topic in cancer research, but also a clinical problem to be solved urgently.

Metronomic chemotherapy is a low-dose, high-frequency mode of continuous administration of antineoplastic drugs without long intermission[15]. The recommended dose is only 1/10-1/3 of the maximum tolerable dose of the drug, so the incidence and intensity of treatment-related side effects are greatly reduced. The antineoplastic mechanism of metronomic chemotherapy is not directed against cancer cells, therefore, it will not produce the problem of drug resistance induced by small doses of drugs. By inhibiting the proliferation and migration of vascular endothelial cells, metronomic chemotherapy is also known as “anti-angiogenesis chemotherapy”[16].

Methods

Aim of the study

The aim of this study is to demonstrate that capecitabine metronomic chemotherapy is non-inferior to capecitabine conventional chemotherapy as maintenance treatment, who have responded to 16-18 weeks first-line chemotherapy in mCRC.

Study design

The study design is a prospective, randomized, open label, phase II clinical trial (Figure 1). Those mCRC patients who respond well, stable disease (SD), partial response (PR) or complete response (CR) according to RECIST Criteria after 16-18 weeks of standard doublet chemotherapy as induction may enrolled into this study, randomly divided into capecitabine metronomic group or standard dosage group. Randomization was done by sealed envelope system. The maintenance treatments are continued until disease progression or severe toxicity. Furthermore, exploratory markers involving angiogenesis (serum VEGF, PDGF, Tie-1 and Tie2, etc) and immune function (CD clusters, serum tumor mutation burden (TMB), etc), are conducted via liquid biopsy (Figure 2).

Study objectives

The duration of disease control after randomization (progression free survival 2, PFS2) is primary endpoint. Meanwhile, progression free survival from induction treatment (PFS1), overall survival (OS), safety and quality of life (QoL) are secondary endpoints.

Study population

The study population consists of patients with unresectable metastatic colorectal cancer, who are scheduled for treatment with first-line doublet chemotherapy. Patients' inclusion and exclusion criteria are defined as follows:

Inclusion criteria:

1. Patients of an age from 18 to 75 years;
2. Histopathologically confirmed colorectal adenocarcinoma and classified as technically unresectable (patients with only local recurrence are not eligible);
3. No prior first line treatment of chemotherapy, radiotherapy, immunotherapy or targeted therapy; Adjuvant chemotherapy is allowed if it has been more than 6 months since the treatment was finished and there have been no signs of disease progression, neither during treatment nor during the 6 months following its completion.
4. Life expectancy > 12 weeks;
5. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 ;
6. At least one measurable lesion for assessment by computed tomography (CT) or magnetic resonance imaging (MRI);
7. Adequate bone marrow function (Hb > 6.0 mmol/L, absolute neutrophil count > $1.5 \times 10^9/L$, platelets > $100 \times 10^9/L$), renal function (serum creatinine $\leq 1.5 \times$ ULN and creatinine clearance, Cockcroft formula, > 30 ml/min), liver function (serum bilirubin $\leq 2 \times$ ULN, serum transaminases $\leq 3 \times$ ULN without presence of liver metastases or $\leq 5 \times$ ULN with presence of liver metastases);
8. Disease evaluation with proven SD, PR or CR according to RECIST after first-line induction treatment before randomization;
9. Written informed consent should be obtained before randomization;

Exclusion criteria:

1. Brain metastasis and with large amounts of pleural and abdominal effusion;
2. Pregnancy or breastfeeding;
3. Disease evaluation with Progression disease (PD) according to RECIST after first-line induction treatment;
4. Previous systemic treatment for advanced disease;
5. Major surgery or radiotherapy (except for antalgic surgery that does not include measurable target lesions) during the 4 weeks prior to inclusion in the study;
6. Participation in another clinical trial with drugs within the previous 30 days;

7. Neoplasm in the 2 years prior to entering the study, except for non-melanoma skin carcinoma or in situ cervix carcinoma;
8. With symptomatic heart disease (arrhythmia, heart failure, or history of myocardial infarction);
9. With active infection, active bleeding or serious metabolic disorder;
10. Signs and symptoms, at the moment of entering the study, of acute or subacute bowel obstruction;
11. Chronic immunological or hormonal treatment, except for hormone replacement treatment at physiological doses.
12. Any geographical or social circumstance or any medical or psychological alteration that, in the investigator's opinion, will not allow the patient to conclude the study.

Study protocol

MDT

Ideally, patients will be discussed by the multi-disciplinary team (MDT) for colorectal cancer from Departments of Surgery, Oncology, Radiology, Pathology, Nutrition and Interventional medicine, etc.) of Ruijin Hospital, Shanghai Jiaotong University School of Medicine, and first-line chemotherapy regimen was formulated by the joint consultation of these experts.

First-line treatment regimens

Standard doublet chemotherapies were used as induction treatment which including mFOLFOX6 regimen (oxaliplatin 85mg/m² iv d1, leucovorin 400mg/m² iv d1, 5-fluorouracil 400mg/m² iv d1, 5-fluorouracil 2400mg/m² CIV 46h, q2w), FOLFIRI regimen (irinotecan 180mg/m² iv d1, leucovorin 400mg/m² iv d1, 5-fluorouracil 400mg/m² iv d1, 5-fluorouracil 2400mg/m² CIV 44h, q2w), XELOX regimen (oxaliplatin 135mg/m² iv d1, capecitabine 1000mg/m² bid po d1-14, q3w), XELIRI regimen (irinotecan 250mg/m² iv d1, capecitabine 1000mg/m² bid po d1-14, q3w). Total first-line treatments were 6 cycles for XELOX/XELIRI regimens, and 8 cycles for mFOLFOX6/FOLFIRI regimens.

Maintenance treatment regimens

Single-agent chemotherapy was used as maintenance treatment which including capecitabine metronomic chemotherapy (capecitabine 500mg bid po), capecitabine conventional chemotherapy (capecitabine 1000mg/m² bid po, d1-14, q3w).

Outcome measurements

Evaluation of tumor response was performed every 8 weeks by the response evaluation in solid tumors criteria (RECIST)[17]. Toxicity was assessed after each cycle by using National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE)[18]. Quality of life was assessed after each cycle by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

Sample size calculation

This project is a non-inferior study. The patients were allocated into capecitabine metronomic chemotherapy group (experimental group) and capecitabine conventional chemotherapy group (control group) by 1:1. The noninferiority margin in PFS was defined at 1.40 in reference to the results of trial reported by H. Y. Luo et al[19]. The HR for capecitabine maintenance group versus observation group in the trial was 0.54 and the reciprocal was 1.85, which leads to 1.43 as 50% retention of 1.85. So, margin of 1.4 was used in this study. Considering a dropout rate of 20%, we estimated that 386 patients (193 in each group) would be needed to achieve 80% power at a one-sided α (significance level) of 0.025.

Statistical analysis

Those patients who do not follow the protocol of their assigned treatment arm will not be analyzed. The statistical analysis will be carried out using SPSS software (version 17.0; SPSS, Chicago, IL, USA). Descriptive statistics will be used for safety evaluation. Mean values and standard deviations (SDs) will be provided for continuous endpoints and frequency and percentage distributions will be provided for discrete data. PFS and OS will be estimated using the Kaplan-Meier method and their medians along with two-sided 95% CIs will be calculated. Comparisons between groups of patients will be made by the log-rank test. All statistical analysis will be carried out at a 5% level significance.

Discussion

Until recently, few mCRC patients could tolerate full doses of chemotherapy longer than 4-6 months, The limitations are mainly due to severe neurotoxicity (oxaliplatin) and chronic diarrhea (irinotecan)[20]. Thus, limiting the duration of the induction chemotherapy to a short period, then exploiting maintenance to prolong disease control at the price of a reasonable toxicity profile, is an appealing strategy for mCRC patients[21].

Lots of studies aimed to reduce the treatment burden and maintain a favorable outcome. OPTIMOX1 trial compared 5FU/LV maintenance treatment with continuous FOLFOX4 regimen in mCRC patients and found that there were no significance in PFS, OS and incidence of adverse events between the two groups, which suggesting that fluorouracil could be used as an alternative maintenance therapy during

the standard regimen treatment without affecting the overall therapeutic effect[22]. MACRO trial compared the efficacy and safety of bevacizumab alone with bevacizumab plus capecitabine and oxaliplatin as maintenance treatment after induction chemotherapy in mCRC patients, which suggests that single-agent bevacizumab as maintenance therapy may be an appropriate option following induction XELOX plus bevacizumab in mCRC patients with mild improvement in PFS[23]. MACRO 2 trial compared the efficacy and safety of cetuximab alone with cetuximab plus mFOLFOX as maintenance treatment after induction chemotherapy in mCRC patients, there were no statistically significant differences in the PFS and OS, the objective response rate and safety profile were also similar. Which suggests that maintenance therapy with single-agent cetuximab following mFOLFOX+cetuximab induction could be a valuable option compared with mFOLFOX+cetuximab treatment continuation[24]. CAIRO3 study reported metronomic capecitabine combined with bevacizumab as maintenance treatment in mCRC patients, it concluded that the PFS of capecitabine metronomic chemotherapy combined with bevacizumab maintenance group was significantly longer than that of the observation group, and the incidence of chemotherapy-related leukopenia, peripheral neurotoxicity and other serious toxic reactions was only increased by 5-10% compared with the observation group, which was completely tolerated by the patients, which has been proved to be an effective and low toxicity maintenance therapy strategy[25]. But bevacizumab is expensive, cost-effectiveness of maintenance capecitabine and bevacizumab for mCRC has been calculated and found that antineoplastic therapy is expensive for payers and society. The price of capecitabine and bevacizumab maintenance therapy should need to be reduced by 93% to make it cost-effective, which restricted the clinical application of this combination regimen as maintenance treatment in mCRC patients.

Xu et al. [19]reported the results of single-agent capecitabine as maintenance therapy after induction first-line chemotherapy of mCRC, the primary endpoint of PFS in capecitabine maintenance group (capecitabine 1000mg/m² bid po, d1-14, q3w) was 6.43 months (95% CI 5.26-7.71), which was significantly longer than the observation group (3.43 months, 95% CI 2.83-4.16), HR=0.54 (0.42-0.70), P<0.001. However, the maximum tolerable dose of capecitabine for maintenance therapy was not adjusted, resulting in the incidence of grade 3/4 toxicity in maintenance treatment group as high as 41%, especially in leukopenia, thrombocytopenia, hand-foot syndrome and mucositis, which was significantly higher than that in observation group.

In recent years, metronomic chemotherapy, as a maintenance therapy strategy for advanced tumors, has been more and more used in clinic and become a new hotspot of anti-cancer therapy. It is a promising strategy for inhibiting angiogenesis and is associated with lower toxicities than conventional chemotherapy[26]. Our previous publication reported that capecitabine metronomic chemotherapy could decrease vascular endothelial growth factor (VEGF) while elevate thrombospondin-1 (TSP-1) expression, an endogenous inhibitor of angiogenesis. And then it could reduce CEP levels and decrease microvessel density (MVD)[27]. Our findings indicated that target angiogenesis rather than drug-sensitive tumor cells was the antitumor effects of capecitabine metronomic treatment in colon cancer cells. With regard to immunomodulation and tumor microenvironments, there were publications reported that metronomic chemotherapy could restore peripheral T-cell proliferation and activate the cytotoxicity of immune effector

cells, which could inhibit tumor progression[28]. Besides this, metronomic chemotherapy could also upregulate dendritic cells to stimulate the proliferation of T lymphocytes[29]. Interestingly, it has been reported that metronomic chemotherapy could result in tumor immunogenicity with antigen processing and presentation genes.

The concepts were emphasized in the design of this study, where a shortened induction phase, limited to 8 instead of 12 cycles (mFOLFOX6/FOLFIRI regimens), 6 instead of 8 cycles (XELOX/XELIRI regimens), followed by two different maintenance strategies. Besides, exploratory markers involving angiogenesis (serum VEGF, PDGF, Tie-1 and Tie2, etc) and immune function (CD clusters, serum tumor mutation burden (TMB), etc) are conducted via liquid biopsy.

In conclusion, this study is a prospective study evaluating whether the effect of capecitabine metronomic chemotherapy as maintenance treatment is non-inferior to capecitabine conventional chemotherapy, who have responded to 16-18 weeks first-line chemotherapy in mCRC. This project intends to study the efficacy and safety of capecitabine metronomic chemotherapy in the maintenance treatment of advanced colorectal cancer, and to explore the strategy of "low toxicity, high efficiency, economy and individualization" which is suitable for China's national conditions and pharmacoeconomics. It has great clinical application prospects and clear socio-economic value.

Trial Status

This is protocol version 20170407. Enrollment started on 29-01-2018, and will last for 36 months. After the start of the study, the first 30 months will consist of inclusion and follow-up of the patients. The last 6 months will consist of follow-up and analysis of results. The study will end at 29-01-2021.

Abbreviations

mCRC, metastatic colorectal cancer; OS, overall survival; SD, stable disease; PR, partial response; CR, complete response; TMB, tumor mutation burden; PFS, progression free survival; QoL, quality of life; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography; MRI, magnetic resonance imaging; PD, Progression disease; MDT, multi-disciplinary team; RECIST, response evaluation in solid tumors criteria; NCI-CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; SDs, standard deviations; VEGF, vascular endothelial growth factor; TSP-1, thrombospondin-1; MVD, microvessel density.

Declarations

Ethics approval and consent to participate

This trial was approved by the Ethics committee of Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine. Written informed consents were obtained from all participants prior to enrollment according to the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this paper.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

This study was conceived and designed by JZ, ZZ, MS. MS, TM, WX, JJ, JW, CZ, CY were responsible for clinical input. MS, JZ drafted the paper. All authors provided significant input to the paper by means of revisions and have read and approved the final manuscript.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018.
2. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut.* 2015; 64: 1637-49.
3. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. *CA Cancer J Clin.* 2017; 67: 177-93.
4. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014; 64: 9-29.
5. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014; 15: 1065-75.
6. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol.* 2004; 22: 23-30.
7. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol.* 2000; 18: 2938-47.
8. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol.* 2001; 19: 2282-92.
9. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med.* 2009; 360: 1408-17.
10. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004; 350: 2335-42.
11. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol.* 2014; 25: 1346-55.
12. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet.* 2000; 355: 1041-7.
13. Bokemeyer C, Bondarenko I, Hartmann JT, de Braud F, Schuch G, Zube A, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol.* 2011; 22: 1535-46.
14. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer:

- updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol*. 2011; 29: 2011-9.
15. Weitman SD, Glatstein E, Kamen BA. Back to the basics: the importance of concentration x time in oncology. *J Clin Oncol*. 1993; 11: 820-1.
  16. Kareva I, Waxman DJ, Lakka Klement G. Metronomic chemotherapy: an attractive alternative to maximum tolerated dose therapy that can activate anti-tumor immunity and minimize therapeutic resistance. *Cancer Lett*. 2015; 358: 100-6.
  17. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000; 92: 205-16.
  18. Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol*. 2003; 13: 176-81.
  19. Luo HY, Li YH, Wang W, Wang ZQ, Yuan X, Ma D, et al. Single-agent capecitabine as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer: randomized clinical trial of efficacy and safety. *Ann Oncol*. 2016; 27: 1074-81.
  20. Berry SR, Cosby R, Asmis T, Chan K, Hammad N, Krzyzanowska MK. Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis. *Ann Oncol*. 2015; 26: 477-85.
  21. Cremolini C, Marmorino F, Bergamo F, Aprile G, Salvatore L, Masi G, et al. Phase II randomised study of maintenance treatment with bevacizumab or bevacizumab plus metronomic chemotherapy after first-line induction with FOLFOXIRI plus Bevacizumab for metastatic colorectal cancer patients: the MOMA trial. *Eur J Cancer*. 2019; 109: 175-82.
  22. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-Go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol*. 2006; 24: 394-400.
  23. Diaz-Rubio E, Gomez-Espana A, Massuti B, Sastre J, Abad A, Valladares M, et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist*. 2012; 17: 15-25.
  24. Aranda E, Garcia-Alfonso P, Benavides M, Sanchez Ruiz A, Guillen-Ponce C, Safont MJ, et al. First-line mFOLFOX plus cetuximab followed by mFOLFOX plus cetuximab or single-agent cetuximab as maintenance therapy in patients with metastatic colorectal cancer: Phase II randomised MACRO2 TTD study. *Eur J Cancer*. 2018; 101: 263-72.
  25. Simkens LH, van Tinteren H, May A, ten Tije AJ, Creemers GJ, Loosveld OJ, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet*. 2015; 385: 1843-52.

26. Klement G, Baruchel S, Rak J, Man S, Clark K, Hicklin DJ, et al. Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. J Clin Invest. 2000; 105: R15-24.

27. Shi H, Jiang J, Ji J, Shi M, Cai Q, Chen X, et al. Anti-angiogenesis participates in antitumor effects of metronomic capecitabine on colon cancer. Cancer Lett. 2014; 349: 128-35.

28. Kaneno R, Shurin GV, Kaneno FM, Naiditch H, Luo J, Shurin MR. Chemotherapeutic agents in low noncytotoxic concentrations increase immunogenicity of human colon cancer cells. Cell Oncol (Dordr). 2011; 34: 97-106.

29. Kaneno R, Shurin GV, Tourkova IL, Shurin MR. Chemomodulation of human dendritic cell function by antineoplastic agents in low noncytotoxic concentrations. J Transl Med. 2009; 7: 58.

Figures

Figure 1

Study design and flowchart.

	First Line treatment	Middle of first line treatment	Enrollment and randomization	During maintenance treatment		After maintenance treatment		
	Before induction treatment (-1 weeks)	After induction treatment (8-9 weeks)	End of induction treatment (16-18 weeks)	After maintenance treatment (every 4 weeks)	After maintenance treatment (every 8 weeks)	When exiting the study (within 1 weeks)	After withdrawal from the study (fourth weeks)	Date of death
Informed consent			※					
Vital signs and physical examination			※	※		※	※	
EORTC QLQ-C30 Form			※	※		※	※	
Liquid biopsy			※		※	※	※	
Routine blood test	※	※	※	※		※	※	
Blood biochemistry	※	※	※	※		※	※	

(blood glucose, liver and kidney function, electrolyte)								
Serum tumor markers (CEA, CA199, CA125, AFP)	※	※	※	※		※	※	
UGT1A1 polymorphism (subjects receiving irinotecan only)	※							
Urine routine	※	※	※	※		※	※	
Stool routine and occult blood	※	※	※	※		※	※	

Coagulation function	※	※	※	※		※	※	
electrocardiogram	※	※	※	※		※	※	
Echocardiography (if electrocardiogram is abnormal)	※							
CT (enhancement) or MRI (enhancement) of chest, abdomen and pelvis	※	※	※		※			
Date and cause of death								※

Figure 2

SPIRIT figure.

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