Original Article

Capecitabine Maintenance Therapy after First-Line Chemotherapy in Patients with Metastatic Colorectal Cancer

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ABSTRACT

Objective: To evaluate the efficacy and toxicity of capecitabine maintenance therapy in metastatic colorectal cancer (mCRC) patients.

Methods: From June 2001 to November 2006, after they had achieved clinical response from first-line chemotherapy, patients with mCRC in our hospital received two different treatment strategies. Thirty-three patients in maintenance group were treated with capecitabine 1000 mg/m^2 po bid d1-14, q21d. Fifty-two patients in non-maintenance group did not receive any further chemotherapy.

Results: Patients in maintenance group and non-maintenance group both received FOLFOX, FOLFIRI and XELOX as first-line therapy. The median chemotherapy cycles the two groups received were the same (6 vs 6). The response rates of first-line chemotherapy were 33.3% in maintenance group and 32.7% in non-maintenance group. Patients in maintenance group received 3−9 cycles of capecitabine therapy (median cycle 4). 29/33 (87.9%) patients in maintenance group and 47/52 (90.4%) in non-maintenance group received following second-line chemotherapy, and no patients underwent targeted therapy. The median survival time and TTP were 40.4 months (95%CI: 24.2−56.6) and 9.0 months (95%CI: 6.7−11.3) in maintenance group, as compared with 21.5 months (95%CI: 14.9−28.0, P=0.015) and 6.5 months (95%CI: 4.4−8.5, P=0.007) in non-maintenance group. No severe adverse event was observed in the capecitabine maintenance group.

Conclusion: mCRC patients could benefit from capecitabine maintenance therapy by prolonging survival time and TTP.

Key words: Maintenance therapy; Metastatic colorectal cancer; Capecitabine

INTRODUCTION

The current management of metastatic colorectal cancer (mCRC) uses fluorouracil-based regimens in combination with either oxaliplatin or irinotecan[1−3]. Although these doublet regimens significantly improve tumor response rate, decisions on the duration of treatment and the number of chemotherapy cycles are made empirically, not evidence-based. Several options including continuing chemotherapy until progression, "stop-and-go" treatment fashion and maintenance therapy have been proposed. OPTIMOX1 and OPTIMOX2 studies showed that LV-5FU maintenance therapy after six cycles of FOLFOX was not inferior to continuing FOLFOX chemotherapy and with less adverse events. Moreover, LV-5FU maintenance therapy significantly improved progression-free survival (PFS) as compared with six cycles of FOLFOX alone[4−7]. Therefore, increasing attention has been drawn to LV-5FU maintenance therapy in mCRC research. Due to its high efficacy, low toxicity and orally taken advantage, capecitabine has emerged as an active agent in CRC treatment. Since limited information on mCRC maintenance therapy has

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been reported, a great interest has been focused on whether capecitabine can replace 5-FU in the maintenance therapy setting. Our present study evaluated whether capacitance maintenance therapy could improve clinical outcome of patients with mCRC.

MATERIALS AND METHODS

Patient Information

Between June 2001 and November 2006, in our hospital, a total of 85 patients with unresectable mCRC received systemic chemotherapy, and the chemotherapy regimens included FOLFOX/ (oxaliplatin-LV-5Fu), XELOX (oxaliplatin-capecitabine) and FOLFIRI (irinotecan-LV-5Fu) with standard dosage and administration method. After disease had achieved control (PR+CR+SD), the patients were divided into capecitabine maintenance therapy group and non-maintenance (observation only) group according to their own choice.

Treatment and Follow-up

After remission, 33 patients in capecitabine maintenance therapy group were treated with capecitabine 1000 mg/m^2, po bid, d 1–14, and the treatment was repeated every 3 weeks. Fifty-two

Table 1. *Demographics and characteristics*

Characteristic	Maintenance group n (%)	Non-maintenance group n (%)	*P* value
Gender			
Male	19 (57.5%)	31 (59.6%)	0.695
Female	14 (42.5%)	21 (40.4%)	
Age (y)			
Range	25–72	35–76	0.630
Median age	61	57	
Primary lesion site			
Colon	21 (63.6%)	34 (65.3%)	0.587
Rectum	12 (36.4%)	18 (34.6%)	
Pathological feature			
Well-differentiated	3 (9.1%)	4 (7.7%)	
Median-differentiated	19 (57.6%)	34 (65.4%)	0.609
Poorly-differentiated	5 (15.1%)	6 (11.6%)	
Unknown	6 (18.2%)	8 (15.3%)	
Metastatic site			
Liver	19 (57.6%)	27 (51.9%)	
Lung	9 (27.3%)	15 (28.8%)	0.234
Others	5 (15.1%)	10 (19.3%)	
Median cycles of 1st-line therapy	6	6	
FOLFOX	25 (75.7%)	36 (69.2%)	
FOLFIRI	5 (15.2%)	9 (17.3%)	0.361
XELOX	3 (9.1%)	7 (13.5%)	
Response rate (%)	33.3%	32.7%	0.987
2nd-line therapy			
Yes	29 (87.9%)	47 (90.4%)	0.634
No	4 (12.1%)	5 (9.6%)	

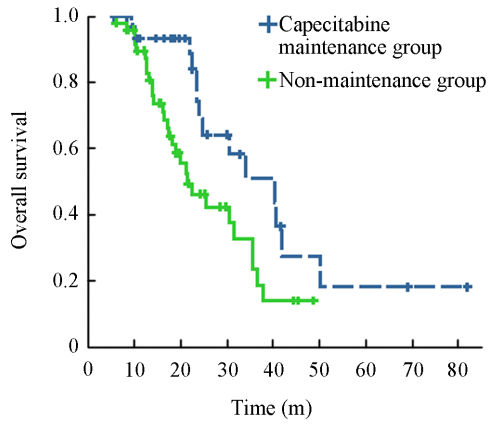

Figure 1. Overall survival curve in mCRC patients by different treatment stratagem.

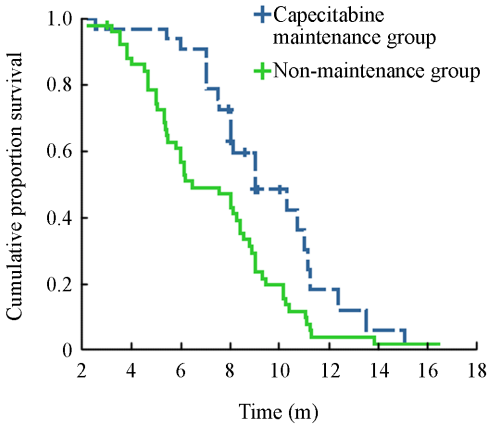

Figure 2. Time to progression curve in mCRC patients by different treatment stratagem.

patients in non-maintenance did not receive further chemotherapy. Patients had complete follow-up visits and measurable lesions that could be evaluated every 3–4 cycles by computed tomography (CT) scan. The last follow-up date was Oct. 1st, 2007.

Chemotherapy response was evaluated according to RECIST criteria. Survival time was calculated from the start of chemotherapy until death or the last follow-up date. Time to progression (TTP) was calculated from the first day of chemotherapy to the occurrence of progression of disease (PD).

Statistical Methods

SPSS13.0 package (Abbott Laboratories, North Chicago, USA) was used for the statistical analysis. The *t* test and chi-square test were used to analyze the characteristics of the groups. The Kaplan-Meier method was used to estimate overall survival (OS) and PFS and the log-rank test was used to compare the curves.

RESULTS

Patient Baseline Characteristics

Within five years, 33 patients were treated with capecitabine as maintenance therapy after first-line chemotherapy. Among 208 patients treated with first-line chemotherapy alone, 52 of them with complete follow-up information were chosen as control group. The baseline characteristics of the two groups were well balanced (Table 1). The median number of capecitabine therapy cycles was 4 (3–9 cycles) in maintenance group. Among them, 87.9% patients undertook second-line chemotherapy, whereas 90.3% patients in non-maintenance group received second-line chemotherapy. If FOLFOX was used in first-line chemotherapy, the second-line regimen would be FOLFIRI and vice versa.

Overall Survival

Until last follow-up on October 1, 2007, the median survival time of maintenance group patients was 40.4 months (95%CI 24.2–56.6) with a range from 5.6 to 81.9 m. Among patients in non-maintenance group, the median OS was 21.9 m (95%CI 14.9–28.0) which was significantly shorter than capecitabine treatment group (P=0.015) (Figure 1).

Time to Progression

The median TTP of maintenance group patients was 9.0 months (95%CI 6.7–11.3) with a range from 2.5–15.1 months. Among patients in non-maintenance group, the median TTP was 6.5 m (95%CI 4.4–8.5) with a range from 2.16 to 16.5 m, which was significantly shortened as compared with capecitabine treatment group (P=0.007) (Figure 2).

Toxicity

Among the 33 patients treated with capecitabine, six patients (18.2%) showed grade 1 hand-foot syndrome; one patient (3%) had grade 3

diarrhea; and one patient (3%) had grade 3 thrombocytopenia. All adverse events were manageable by supportive care. The drug-induced toxicity did not interrupt capecitabine treatment or additional therapy after disease progression.

DISCUSSION

5-Fu and its derivatives, irinotecan and oxaliplatin are three active drugs in mCRC management. These three cytotoxic drugs used either in combination or as single agent in a sequential order can significantly improve the clinical outcome of patients with advanced CRC[8−10]. It has always been a dilemma to decide the following treatment plan for patients who achieve disease control after first-line chemotherapy. In current clinical practice, some patients are recommended to stop further chemotherapy until disease progression; others are recommended to continue to receive the same intensive treatment until disease progression or intolerance to drug toxicity. Recently, a "stop-and-go" approach has been validated in large-scale clinical trials and employed in mCRC treatment. Several questions associated with this new approach have been raised. These questions include: first-line therapy duration, a complete therapy stop or maintenance therapy after firs-line therapy, and drug selection and timing for maintenance therapy[11, 12].

Maintenance therapy has been widely used in hematological malignancy treatment after induction chemotherapy or hematopoietic stem cell transplantation. Recent investigations showed that maintenance therapy in non-small cell lung cancer and colorectal cancer may prolong progression-free survival[13−15]. OPTIMOX1 study demonstrated that regarding to PFS, stopping six cycles followed by LV-5FU alone achieved the same efficacy results as continuing FOLFOX regimen until progression or occurrence of severe adverse event(s), meanwhile oxaliplatin reduction lowered the risk of severe toxicity[4]. Subsequent OPTIMOX2 showed that LV-5FU maintenance therapy was superior to the complete discontinuation of FOLFOX after six cycles in regard to disease control period[5]. These results raised a possibility to use LV-5FU as maintenance therapy in mCRC. 5-FU continuous infusion requires central venous catheter and this invasive procedure increases the risks of infection, thrombosis and bleeding. Capecitabine (Xeloda) is an orally-administered pro-drug that is converted to 5-FU in a serial 3-step enzymatic reaction. 5-Fu inhibits DNA synthesis by forming complex with thymidylate synthetase (TS) which is primarily expressed in tumor tissues. Therefore, the oral capecitabine is selectively concentrated in tumor cells and reduces the cytotoxic risks to normal tissues[16, 17]. Moreover, several lines of evidences have suggested that the efficacy of capecitabine is not interior to 5-FU in the treatment of CRC[18−26]. Based on these findings, further study on the role of capecitabine in maintenance therapy is warranted.

In our current study, capecitabine was used in maintenance therapy after patients achieved disease control by initial chemotherapy. The number of median cycles of capecitabine therapy was 4. The median number of first-line therapy was 6. Both maintenance group and non-maintenance group received second-line chemotherapy after disease progression. The TTP and OS of patients treated with capecitabine in maintenance group were significantly longer than those of patients in non-maintenance group (P<0.01). In addition, the mild capecitabine drug-related toxicity did not cause treatment discontinuation or delayed second-line therapy. These results indicate that capecitabine therapy can bring extra clinical benefit to mCRC patients. In our study, we also noticed that most patients experienced more severe drug-associated adverse events during the sixth cycle of firs-line chemotherapy than prior cycle. This observation suggests that either a complete stop of the treatment or a change to maintenance therapy should be taken into consideration after 6 cycles of intensive first-line treatment. Previous study already suggested that a complete stop of treatment compromise the OS of mCRC patients. It would be wise to switch to maintenance therapy for patients who are still with good performance status after first-line therapy. Since the number of median cycle of capecitabine therapy was 4, it is suggestive that the maintenance therapy would bring survival benefit to patients receiving 4 cycles of capecitabine therapy. However, after 4 cycles of capecitabine therapy, the choice between continuing maintenance therapy and stopping treatment until disease progression is still unknown and requires large-scale randomized trials.

Given the results of the present study, we conclude that capecitabine is an alterative option for maintenance therapy in mCRC patients.

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