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ORIGINAL ARTICLE

Capecitabine combined with bevacizumab in maintenance therapy of metastatic colorectal cancer: a retrospective clinical study

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Summary

Purpose: *To explore the clinical efficacy and safety of capecitabine combined with bevacizumab, capecitabine monotherapy, and bevacizumab monotherapy in the maintenance therapy of metastatic colorectal cancer after first-line chemotherapy.*

Methods: *The clinical data of 147 patients with pathologically confirmed colorectal cancer in stage $T_XN_XM_1$ were retrospectively analyzed. The patients were firstly treated with 4-6 cycles of standard first-line chemotherapy. After the disease condition was evaluated as remission or stability, capecitabine and/or bevacizumab was used for maintenance therapy. All the patients were treated with drugs until the disease progressed or intolerable adverse drug reactions emerged. The progression-free survival (PFS), overall survival (OS), adverse drug reactions, and quality-of-life scores were compared among the three groups.*

Results: *The median PFS (mPFS) and mOS of patients in the combined treatment group, capecitabine group and bevacizumab group were 7.5 months and 25.8 months, 4.9 months and 24.4 months, and 5.7 months and 25.1 months, respectively. The results of log-rank test revealed that the PFS of the combined treatment group was significantly longer than in the capecitabine group and bevacizumab group ($p=0.043$, $p=0.046$). However, there was no statistically significant difference in the PFS between the capecitabine and bevacizumab group ($p=0.889$). Besides, no statistically significant difference was observed in the OS among the three groups ($p=0.366$). The common adverse reactions during treatment mainly included fatigue, nausea and vomiting, diarrhea, hematologic toxicity, impairment of liver and kidney function, hypertension, bleeding, sensory neuropathy, mucositis, and hand-foot syndrome. The combined treatment and the capecitabine group had a higher incidence rate of hand-foot syndrome than bevacizumab group ($p=0.007$), and the incidence rate of bleeding was higher in the combined treatment and the bevacizumab group than that in the capecitabine group ($p=0.027$). No statistically significant differences were found in the incidence rates of other adverse reactions ($p>0.05$). In addition, there were no statistically significant differences in the quality-of-life scores (assessed using the EORTC-QLQ-C30 scale) among the three groups ($p>0.05$).*

Conclusions: *Capecitabine combined with bevacizumab is safe and effective in the maintenance therapy of metastatic colorectal cancer, and can significantly prolong the PFS. The drugs are well tolerated, and the patients' quality of life is not affected.*

Key words: *capecitabine, bevacizumab, colorectal cancer, maintenance therapy*

Introduction

As one of the most common malignant tumors, colorectal cancer ranks third in morbidity and fourth in mortality. About 60% of colorectal cancer patients are diagnosed at an advanced stage, and their 5-year survival rate is about 13% [1,2]. The current standard first-line chemotherapy regimen for metastatic colorectal cancer (mCRC) is the combination of two drugs based on 5-fluorouracil (5-FU), which is combined with molecular targeted therapy [3].

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In recent years, mounting clinical studies have suggested that maintenance therapy with low-intensity and low-dose drugs for mCRC patients benefiting from first-line chemotherapy can prolong the time of disease control and ameliorate the quality of life of patients [4-6]. However, at present, no standard maintenance therapy has been recommended in the NCCN guidelines.

The present study aimed to compare the efficacy and safety of capecitabine combined with bevacizumab, capecitabine monotherapy and bevacizumab monotherapy in the maintenance therapy of patients with mCRC, so as to provide a basis for clinical treatment.

Methods

General data

The clinical data of 147 patients with stage IV colorectal cancer confirmed by pathology or cytology (*the 7th edition of the AJCC Cancer Staging Manual*) were retrospectively analyzed. *The inclusion criteria* involved: (1) patients aged 18-75 years old, (2) those with Eastern Cooperative Oncology Group (ECOG) score of 0-2 points, (3) those with ≥1 measurable lesions according to the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1, and (4) those whose estimated survival was >3 months. *The exclusion criteria* were as follows: (1) patients whose disease condition was evaluated as progressive disease (PD) after basic chemotherapy, or (2) those with underlying diseases such as severe heart, liver or kidney diseases, or other malignant tumors.

All the patients were treated with XELOX regimen (capecitabine + oxaliplatin) or FOLFOX regimen (fluorouracil + calcium folinate + oxaliplatin) with or without bevacizumab for 12-24 weeks. After evaluation of disease condition, patients with complete response (CR), partial response (PR), and stable disease (SD) were treated with capecitabine + bevacizumab (n=49), capecitabine (n=49), and bevacizumab (n=49), respectively, until the drugs were intolerable or the disease progressed. No statistically significant differences were found in the baseline data of patients, such as age, sex, tumor location, tumor metastasis and ECOG score (p>0.05, Table 1), which were comparable. All the patients enrolled were informed of the study according to the Declaration of Helsinki, and signed the inform consent form.

Treatment methods

Patients in the capecitabine + bevacizumab group (combined treatment group) took oral capecitabine (Shanghai Roche Pharmaceutical Co., Ltd., NMPN: H20073024, specification: 0.5 g/tablet) at 1000 mg/m^2, twice a day, for 14 consecutive days, and then the drugs were stopped for 1 week (3 weeks as one cycle). Later, they received intravenous infusion of bevacizum-

Table 1. Baseline characteristics of the studied patients

Parameters	*Combination group (n=49)* n (%)	*Capecitabine group (n=49)* n (%)	*Bevacizumab group (n=49)* n (%)	*p value*
Age (years)	57.3±7.7	55.7±6.9	56.8±7.4	0.545
Gender				0.428
Male	29 (59.2)	33 (67.3)	35 (71.4)	
Female	20 (40.8)	16 (32.6)	14 (28.6)	
BMI (kg/m^2)	22.4±3.3	23.3±3.5	21.8±3.1	0.081
Location of primary tumor				0.417
Colon	34 (69.4)	30 (61.2)	36 (73.5)	
Rectum	15 (30.6)	19 (38.8)	13 (26.5)	
Number of metastatic sites				0.723
1	25 (51.0)	29 (59.2)	30 (61.2)	
2	17 (34.7)	14 (28.6)	11 (22.4)	
≥3	7 (14.3)	6 (12.2)	8 (16.3)	
Metastatic organ				0.514
Liver	19 (38.8)	24 (49.0)	21 (42.9)	
Lung	16 (32.7)	14 (28.6)	13 (26.5)	
Bone	6 (12.2)	5 (10.2)	7 (14.3)	
Peritoneal implantation	8 (16.3)	6 (12.2)	8 (16.3)	
ECOG score (points)				0.612
0	28 (57.1)	25 (51.0)	29 (59.2)	
1	15 (30.6)	17 (34.7)	13 (26.5)	
2	6 (12.2)	7 (14.3)	7 (14.3)	

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group.

ab (Roche Pharma Ltd., approval number: S20170035, specification: 100 mg/vial) at 7.5 mg/kg, once every 3 weeks. Patients in the capecitabine group were given oral capecitabine at 1000 mg/m^2, twice a day, for 14 consecutive days, and then the drug was stopped for 1 week (3 weeks as one cycle). Patients in the bevacizumab group received intravenous infusion of bevacizumab (7.5 mg/kg, diluted with 0.9% sodium chloride) for 30-90 min once every 3 weeks. The three groups of patients received maintenance therapy until the drug reactions were intolerable, the disease condition was evaluated as PD, or the drugs were stopped for any reason.

Observation indexes

CT or MRI scan were applied to assess the efficacy during maintenance therapy and follow-up, and bone marrow, liver and kidney functions were evaluated in each cycle of maintenance therapy. The survival of patients was recorded, progression-free survival (PFS) was defined as the duration from the start of maintenance therapy to PD or death of patient, and overall survival (OS) was defined as the duration from the start of combined chemotherapy to death from any cause. The incidence rates of hematologic toxicity, impairment of liver and kidney function, gastrointestinal reaction, hand-foot syndrome and bleeding were calculated according to the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. The quality of life of the patients was assessed using the Quality of Life Questionnaire Core 30 version 3.0 (QLQ-C30 v3.0) of the European Organization for Research and Treatment of Cancer (EORTC).

Statistics

SPSS 22.0 was utilized for statistical analyses. The measurement data were expressed as mean ± standard deviation ($\overline{x}$±s), and two-sample t-test was performed for intergroup comparison. The enumeration data were expressed as rate (%), and x^2 test was conducted for intergroup comparison. Kaplain-Meier method was performed to plot the survival curves, and log-rank test was employed to compare the difference in survival rate between groups. P<0.05 indicated that the difference was statistically significant.

Results

Comparison of efficacy among the three groups of patients

The patients were followed up for 3-36 months. The median PFS (mPFS) and mOS of patients in the combined treatment group, capecitabine group, and bevacizumab group were 7.5 months and 25.8 months, 4.9 months and 24.4 months, and 5.7 months and 25.1 months, respectively. The survival curves of patients were plotted using the Kaplain-Meier method (Figure 1), and examined by log-rank test. It was found that the PFS in the combined treatment group was significantly longer than in the capecitabine group and bevacizumab group (p=0.043, p=0.046). However, there was no statistically significant difference in the PFS between the capecitabine group and bevacizumab group (p=0.889). Besides, no statistically significant difference was found in the OS among the three groups (p=0.366). After the first progression in the combined treatment group, 12 patients received chemotherapy again, 5 patients received the XELOX/FOLFOX regimen again, and 7 patients were shifted to the FOLFIRI regimen (including 1 case combined with bevacizumab, 2 cases combined with cetuximab, and 2 cases combined with apatinib). In addition, another 7 patients received local therapy such as radiofrequency ablation for multiple liver lesions. After the first progression

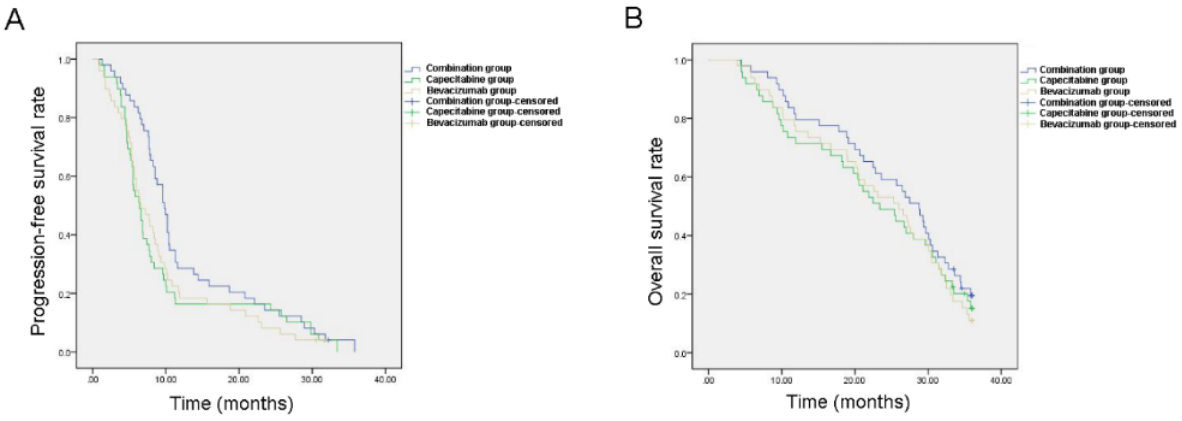

Figure 1. Kaplan-Meier survival curves of patients in the combination group, capecitabine group and bevacizumab group. **A:** The difference between progression-free survival rate of patients in the combination group was significantly higher than those of capecitabine group and bevacizumab group (p=0.043, p=0.046). The difference between progression-free survival rate of patients in capecitabine group and bevacizumab group had no statistically significant difference (p=0.889). **B:** The difference between overall survival rate of patients in the combination group, capecitabine group and bevacizumab group was not statistically significant (p=0.366).

in the capecitabine maintenance therapy group, 16 patients received chemotherapy again, 8 patients received the XELOX/FOLFOX regimen again, and 8 patients were shifted to the FOLFIRI regimen (including 2 cases combined with cetuximab, and 3 cases combined with apatinib). In addition, another 6 patients received local therapy such as radiofrequency ablation for multiple liver lesions. After the first progression in the bevacizumab maintenance therapy group, 13 patients received chemotherapy again, 5 patients received the XELOX/SOX regimen combined with bevacizumab chemotherapy, 5 patients were shifted to the FOLFIRI regimen + bevacizumab chemotherapy, and 3 patients received FOLFIRI regimen + cetuximab chemotherapy. In addition, another 2 patients received radiofrequency ablation for multiple liver lesions.

Incidence of adverse reactions in the three groups of patients

During treatment, the common adverse reactions mainly included fatigue, nausea and vomiting, diarrhea, hematologic toxicity, impairment of liver and kidney function, hypertension, bleeding,

Table 2. Comparison of adverse reactions of patients in the three studied groups

	Combination group (n=49) n (%)	*Capecitabine group (n=49)* n (%)	*Bevacizumab group (n=49)* n (%)	*p value*
Fatigue	14 (28.6)	11 (22.4)	9 (18.4)	0.483
Nausea and vomiting	19 (38.8)	13 (26.5)	10 (20.4)	0.123
Diarrhea	9 (18.4)	5 (10.2)	4 (8.2)	0.265
Anemia	16 (32.7)	14 (28.6)	11 (22.4)	0.449
Leukopenia	18 (36.7)	17 (34.7)	15 (30.6)	0.709
Thrombocytopenia	10 (20.4)	9 (18.4)	8 (16.3)	0.773
Liver /Renal function impairment	11 (22.4)	10 (20.4)	13 (26.5)	0.665
Hypertension	9 (18.4)	6 (12.2)	8 (16.3)	0.597
Bleeding	9 (18.4)	8 (16.3)	1 (2.0)	0.027
Sensory neuropathy	20 (40.8)	17 (34.7)	23 (46.9)	0.468
Mucositis	3 (6.1)	2 (4.1)	1 (2.0)	0.594
Hand-foot syndrome	16 (32.7)	15 (30.6)	4 (8.2)	0.007

Table 3. Comparison of posttreatment EORTC-QLQ-C30 scale scores of patients in the three studied group

Parameters	*Combination group (n=49)*	*Capecitabine group (n=49)*	*Bevacizumab group (n=49)*	*p value*
QLQ-C30				
Functioning scales				
Physical	67.31±13.31	70.96±14.40	71.07±13.79	0.313
Role	53.81±15.54	58.67±16.11	59.69±15.58	0.146
Emotional	67.73±18.84	66.42±17.59	65.56±16.89	0.732
Social	63.61±15.75	63.39±13.94	64.64±13.70	0.726
Cognitive	78.36±18.58	79.79±17.83	81.01±17.95	0.669
General health status	55.46±14.15	57.61±16.51	58.17±13.04	0.527
Symptom scales				
Appetite loss	27.73±21.15	25.48±20.31	24.52±19.03	0.522
Constipation	20.64±12.29	15.36±12.40	16.17±13.34	0.089
Dyspnea	29.34±12.48	24.96±13.66	26.92±15.39	0.298
Fatigue	45.34±18.56	43.74±14.95	42.21±19.22	0.582
Financial problems	28.58±17.44	29.16±17.88	26.63±18.33	0.665
Nausea / vomiting	10.88±15.48	9.71±10.73	8.03±11.83	0.545
Diarrhea	20.33±9.53	18.14±8.89	16.86±9.29	0.175
Pain	29.39±13.75	26.62±13.84	25.83±14.77	0.426
Insomnia	33.98±15.65	30.45±14.60	31.68±13.53	0.481

EORTC: European Organization for Research and Treatment of Cancer.

sensory neuropathy, mucositis and hand-foot syndrome. Most of the adverse reactions were grade I-II, grade III was rare, and no grade IV adverse reactions were observed. After timely and appropriate symptomatic treatment, all of the adverse reactions were improved, without affecting the treatment. The incidence rate of hand-foot syndrome was higher in the combined treatment group and capecitabine group (p=0.007), and the incidence rate of bleeding was higher in the combined treatment group and bevacizumab group (p=0.027). There were no statistically significant differences in the incidence rates of other adverse reactions (p>0.05) (Table 2).

Patient quality of lifes

After treatment, no statistically significant differences were found in the scores of physical function, role function, emotional function, social function, cognitive function and global health status (assessed using the QLQ-C30 scale) among the three groups (p>0.05). Besides, no statistically significant differences were observed in the scores of symptoms of fatigue, appetite loss, dyspnea, nausea and vomiting, diarrhea, constipation, pain, insomnia and financial difficulties among the three groups (p>0.05). These results suggested that capecitabine combined with bevacizumab will not affect the patient overall quality of life (Table 3).

Discussion

The morbidity and mortality rates of colorectal cancer show an upward trend annually. At present, the commonly adopted chemotherapeutic drugs for advanced colorectal cancer consist of fluorouracil, oxaliplatin and irinotecan, and the major targeted drugs include bevacizumab and cetuximab. Although combined treatment can prolong the PFS of patients by 9-11 months, and prolong the OS even by 2 years, with the extension of chemotherapy time, the adverse reactions cumulated and only 1/3 of the patients can adhere to the treatment until PD [7,8]. After the patients completed the planned initial chemotherapy cycles and their disease condition reached CR/PR/SD, continuous maintenance therapy with low-dose and low-toxic drugs can not only delay the progression and metastasis of the tumor, but also reduce the side effects of the drugs [9,10]. Currently, maintenance therapy has become the major treatment mode for advanced mCRC after first-line chemotherapy. Nevertheless, the best maintenance therapy for mCRC is still controversial. Currently, the most commonly used regimen is bevacizumab + fluorouracil, or maintenance therapy with bevacizumab or fluorouracil [11].

Due to convenient administration and good patient compliance, capecitabine is commonly adopted in the maintenance therapy of colorectal cancer. A phase III, open-label, multicenter, randomized clinical trial demonstrated that the mPFS of patients in the capecitabine maintenance therapy group was remarkably prolonged in contrast with that of patients in the observation group (also drug withdrawal group), and the most common grade 3 or 4 toxicities were neutropenia, hand-foot syndrome, and mucositis [12]. Bevacizumab, a recombinant humanized monoclonal antibody, can selectively bind to VEGF and block its activity, thus reducing neovascularization and suppressing tumor growth [13]. In the CAIRO3 study, 556 mCRC patients who received late first-line treatment with XELOX + bevacizumab were assigned to capecitabine + bevacizumab maintenance therapy group and drug withdrawal group (also observation group) at a ratio of 1:1. The results showed that the mPFS of patients in the maintenance therapy group was significantly prolonged compared with those in the drug withdrawal group (11.7 months *vs.* 8.5 months, p<0.0001). Although the incidence rate of hand-foot syndrome increased in the maintenance therapy group (64% *vs.* 23%), the drugs were well tolerated [14]. The efficacy and safety of capecitabine + bevacizumab maintenance therapy were evaluated in another multi-center, single-arm, phase II study (CCOG-0902) [15,16]. In that study, the researchers also believed that XELOX + bevacizumab, capecitabine + bevacizumab, and XELOX + bevacizumab are feasible first-line maintenance therapy modes for Japanese mCRC patients.

In the AIO 0207 trial, the efficacy and safety of capecitabine + bevacizumab and capecitabine alone for maintenance therapy were compared. A total of 427 patients received 5-FU/capecitabine + bevacizumab maintenance therapy or bevacizumab maintenance therapy, or had drug withdrawal after XELOX/FOLFOX + bevacizumab treatment. The results showed that the PFS1 and PFS2 in the combined maintenance therapy group, single drug maintenance therapy group and drug withdrawal group were 6.2 months and 6.9 months, 4.8 months and 6.1 months, and 3.6 months and 6.4 months, respectively (p=0.056), indicating that single drug maintenance therapy is not inferior to combined maintenance therapy [17]. Another quality of life analysis of the AIO 0207 trial demonstrated that active maintenance therapy with 5-FU/capecitabine + bevacizumab after induction therapy brings no harmful effect on the quality of life score compared with the maintenance therapy group or observation group [18]. Hence, the maintenance therapy with capecitabine + bevacizumab may be the first

choice after induction therapy with XELOX/FOLFOX+ bevacizumab.

In this study, capecitabine + bevacizumab, capecitabine monotherapy and bevacizumab monotherapy were used in the maintenance therapy of mCRC. The follow-up results revealed that the PFS in the combined treatment group was significantly longer than in the capecitabine group and bevacizumab group (p=0.043, p=0.046). Besides, there was no statistically significant difference in the PFS between the capecitabine and bevacizumab group (p=0.889), and in the OS among the three groups (p=0.366). All the adverse reactions occurring during treatment were improved after timely and appropriate symptomatic treatment, without affecting the treatment. The combined treatment and capecitabine group had a higher incidence rate of hand-foot syndrome than the bevacizumab group (p=0.007), and the incidence rate of bleeding was higher in the combined treatment and bevacizumab group than in the capecitabine group (p=0.027). No statistically significant differences were found in the incidence rates of other adverse reactions (p>0.05). These results suggested that the combination of drugs did not significantly elevate the incidence rates of adverse reactions, and the drugs were well tolerated by patients. In addition, there was no obvious difference in the quality of life score (evaluated using the EORTC-QLQ-C30 scale) among the three groups, which was in agreement with previous literature reports, indicating that the combination of drugs had no remarkable influence on the quality of life of patients.

There were many shortcomings in this study. For example, the sample size was small, the follow-up time was short, and the follow-up content was not comprehensive enough. In the future, further multi-center, large-sample, randomized controlled trials are needed to verify the conclusions of this study.

Conclusions

Capecitabine combined with bevacizumab is safe and effective for the maintenance therapy of mCRC, which can dramatically prolong the PFS. The drugs are well tolerated, and the patients' quality of life is not affected.

Conflict of interests

The authors declare no conflict of interests.

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