


Research Paper

The Efficacy of Bevacizumab in Different Line Chemotherapy for Chinese Patients with Metastatic Colorectal Cancer

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Abstract

Objective: To evaluate the effect of bevacizumab in different lines for Chinese patients with metastatic colorectal cancer (mCRC).

Methods: Patients of mCRC treated with bevacizumab or not at Sun Yat-sen University Cancer Center from 2007 to 2013 were recruited as study and control group. Endpoints were overall survival (OS), progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR). Corresponding survival rates of first- and second-line in study and control group were compared.

Results: 1. Median OS of study and control group were 44.8 (95% CI: 37.1~52.4) months, 36.1 (95% CI: 32.8~39.5) months respectively, which were significantly different ($P=0.004$). 2. In the first line treatment, median OS of study and control group were 49.9(95% CI: 40.1~59.8) months and 36.1 (95% CI: 32.7~39.4) months ($P=0.002$), respectively. And median PFS were 10.1(95% CI: 8.7~11.5) months and 6.2 (95% CI: 5.5~6.8) months ($P<0.001$), respectively. 3. In the second line treatment, median OS of study and control group were 34.8 (95% CI: 26.3~43.3) months and 24.6 (95% CI: 22.2~27.0) months ($P=0.022$), respectively. And the mPFS were 6.3 (95% CI: 4.7~7.8) months and 3.1 (95% CI: 2.5~3.6) months ($P<0.001$), respectively. 4. Median OS of first- and second-line treatment of the study groups were 49.9(95% CI: 40.1~59.8) months and 34.8 (95% CI: 26.3~43.3) months ($P=0.189$), respectively.

Conclusion: The combination of bevacizumab and chemotherapy had a promising efficacy in Chinese mCRC patients. However, their OS were statistically insignificant between first- and second-line of bevacizumab groups.

Key words: bevacizumab; chemotherapy line setting; mCRC; efficacy.

Introduction

Bevacizumab, the classical anti-angiogenesis drug, had been expected to both prune the immature vessels and normalize tumor vessels by decreasing interstitial fluid pressure and increasing the delivery

of drugs and oxygen^[1]. It had been approved by the US Food and Drug Administration (FDA) to be used in various cancers such as metastatic colorectal cancer (mCRC)^[2-7], advanced non-small cell lung cancer

(NSCLC)^[8, 9], advanced renal cell carcinoma^[10, 11], metastatic breast cancer^[12, 13] and so on.

In metastatic colorectal cancer (mCRC), bevacizumab was widely used in the first-^[2, 6], second-^[7], later-line treatment^[14] and even progression beyond its failure^[15]. However, the administration of bevacizumab had always been challenged. Though both of PFS and OS were improved significantly in AVF2017, ARTIST, and E3200 trials^[2, 3, 7], the original short OS of IFL regimen in the former two trials weakened their significances. Moreover, only PFS rather than OS was significantly improved in the NO16966 trial^[16], which was also the main reason of FDA withdrawing the license of bevacizumab when combined with paclitaxel in the first line setting of metastatic breast cancer^[17-20].

Bevacizumab is available in the treatment of first-, second-, later-line and even beyond its initial disease progression for mCRC, and the efficacy might increasing with treatment course. However, not all patients had the opportunity to receive bevacizumab treatment. In the developing countries and the countries with incomplete health insurance, mCRC patients could only receive the expensive drug in just one-line of the whole treatment. Then, the current question is that which line therapy is more beneficial with the combination of bevacizumab? Current researches of it had not been found yet. A previous study of us had analyzed a small sample of Chinese mCRC, the result showed that the OS of bevacizumab combined group is much more longer than chemotherapy alone group, while it had no statistically difference between the first- and second-line of bevacizumab combined treatment^[21]. The current study expanded the sample size and prolonged the follow-up time, and the aim of it is not only to confirm our previous result but also offer some valuable data to the mCRC patients with limited opportunity to receive bevacizumab treatment.

Materials and methods

Study population

Patients who met the following criterions were selected as study group: 1) Diagnosed as mCRC based on pathological specimens of the primary tumor, at the same time with clinical and/or pathological evidences of distant metastasis lesion, at the Sun Yat-sen University Cancer Center from 2007 to 2013 and finished the entire course of first- and second-line chemotherapy in this center 2) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 ; 3) Bevacizumab was added to the palliative regimens including oxaliplatin-based, irinotecan-based regimens and so on; 4) More than 4 cycles of

bevacizumab was required, since 4 cycles was considered the minimum course for the patients got benefit from bevacizumab in our previous study^[22]. Meanwhile, the consecutive mCRC patients in the control group met the same criterions with the study group except for bevacizumab administration. The exclusion criterions of both groups included 1) No pathological diagnosis; 2) Unclear medical histories; 3) Bevacizumab beyond its initial disease progression^[15].

Evaluation of efficacy

The short-term effect was evaluated by the independent group based-on criterion of RESIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors): overall response rate (ORR), disease control rate (DCR); the long-term efficacy was evaluated by comparing overall survival (OS) and progression free survival (PFS).

Assessment

Patients' OS, PFS, ORR and DCR were the primary statistical endpoints of the study. OS was calculated from diagnosis to death or the date of last follow-up (December 25th, 2015), and PFS was deemed to be the period from the initial treatment of bevacizumab to the progression date by imaging examination according to the RECIST 1.1 criteria.

Statistical analyses

Survival curves were estimated using the Kaplan-Meier method. All the statistical analysis was conducted by SPSS 18.0 software package and the P value less than 0.05 was considered with statistically significant.

Follow up

The last follow-up was conducted on December 25th, 2015 through telephone interview or medical records review. All the patients in the study and the control group were followed up closely by then.

Human Rights

All the patients' information in our study has got IRB Approval of our hospital.

Results

Patient characteristics and therapeutic regimens

There were 82 patients entered the study group, all of them received bevacizumab (5 mg/kg, every two weeks) combined with chemotherapy in first- or second-line treatment. In the first-line of study group, there were 29 and 31 patients treated with oxaliplatin-based (FOLFOX and XELOX) and

irinotecan-based (FOLFIRI, IFL, CPT-11 plus xeloda) chemotherapy, respectively; the median cycles of bevacizumab were 9.62 (ranged from 4~25). In the second-line treatment, 12 and 10 patients were treated with oxaliplatin-based and irinotecan-based chemotherapy, respectively; the median cycles of bevacizumab were 6.86 (ranged from 4~15). While in the first- and second-line of control group, 446 patients were treated with chemotherapy alone. Patients were treated with oxaliplatin-based, irinotecan-based and other chemotherapy as well, which is shown in Table 3. All the patients' characteristics and potential prognostic factors including sex, age, tumor location, pathological type and receiving third-line treatment or not were balanceable between the study group and the control group (Table 1). In the study group, 98.8% (81/82) and 42.7% (35/82) patients exhibited progressed and died, and 100% (446/446) patients and 64.6% (288/446) patients exhibited progressed and died in the control group (Table 2).

Table 1. Patient baseline characteristics in the study and the control group.

Patient characteristics	Control group	Study group	P*		
			1	2	3
Number	446	82			
Gender					
Male	297 (66.6%)	53 (64.6%)	0.730	0.325	0.213
Female	149 (33.4%)	29 (35.4%)			
Age (years)					
Median (range)	54 (16~84)	53 (20~78)	0.181	0.154	0.820
≤65	352 (78.9%)	70 (85.4%)			
>65	94 (21.1%)	12 (14.6%)			
Primary tumor					
Colon	295 (66.1%)	55 (67.1%)	0.870	0.583	0.222
Rectum	151 (33.9%)	27 (32.9%)			
Pathological type					
Adenocarcinoma	413 (92.6%)	77 (93.9%)	0.675	0.907	0.628
Others	33 (7.4%)	5 (6.1%)			
Accepted three-line treatment			0.676	0.478	0.791
Yes	106 (23.8%)	21 (25.6%)			
No	340 (76.2%)	61 (74.4%)			

Study group: the group of patients receiving bevacizumab.

Control group: the group of patients not receiving bevacizumab.

P*1: the balance test P value of total patients.

P*2: the balance test P value of the first-line regimen.

P*3: the balance test P value of the second-line regimen.

Efficacy of bevacizumab in different lines

In the entire group, the median OS of the study and the control group were 44.8 (95% CI: 37.1~52.4) months, 36.1 (95% CI: 32.8~39.5) months (P=0.004), respectively (Fig.1).

The median OS of study group and control group in the first-line were 49.9(95% CI: 40.1~59.8) months and 36.1 (95% CI: 32.7~39.4) months

(P=0.002); in the second-line were 34.8 (95% CI: 26.3~43.3) months and 24.6 (95% CI: 22.2~27.0) months (P=0.022), respectively (Fig.2, Fig.3).

The median PFS of the study group and control group in the first-line were 10.1(95% CI: 8.7~11.5) months and 6.2 (95% CI: 5.5~6.8) months (P<0.001); in the second-line were 6.3 (95% CI: 4.7~7.8) months and 3.1 (95% CI: 2.5~3.6) months (P<0.001), respectively (Fig.4, Fig.5).

In the study group, the median OS of the first- and second-line treatment were 49.9(95% CI: 40.1~59.8) and 34.8 (95% CI: 26.3~43.3) months (P=0.189), respectively (Fig.6). The ORR were 30% (18/60), 22.7% (5/22); DCR were 63.3% (38/60), 59.1% (13/22) (P=0.359), respectively (Table 2).

Table 2. The efficacy of bevacizumab in the study group.

Patient characteristics	Bevacizumab group	
	First-line	Second-line
Number	60	22
ORR (%)	30% (18/60)	22.7% (5/22)
DCR (%)	63.3% (38/60)	59.1% (13/22)
PFS (months)	10.1(95% CI: 8.7~11.5)	6.3 (95% CI: 4.7~7.8)
OS (months)	49.9(95% CI: 40.1~59.8)	34.8 (95% CI: 26.3~43.3)

Table 3. The first and second-line chemotherapy regimen of control and study group

Patient characteristics	First-line		Second-line	
	Control	Study	Control	Study
Number	446	60	163	22
Oxaliplatin based	357	29	41	12
Irinotecan based	75	31	113	10
Other chemotherapy	14	0	9	0

Study group: the group of patients receiving bevacizumab; oxaliplatin-based: FOLFIFOX, XELOX; irinotecan-based: FOLFIRI, IFL, CPT-11+xeloda.

Control group: the group of patients not receiving bevacizumab; oxaliplatin-based: FOLFIFOX, XELOX, oxaliplatin+S-1; irinotecan-based: FOLFIRI, CPT-11+S-1

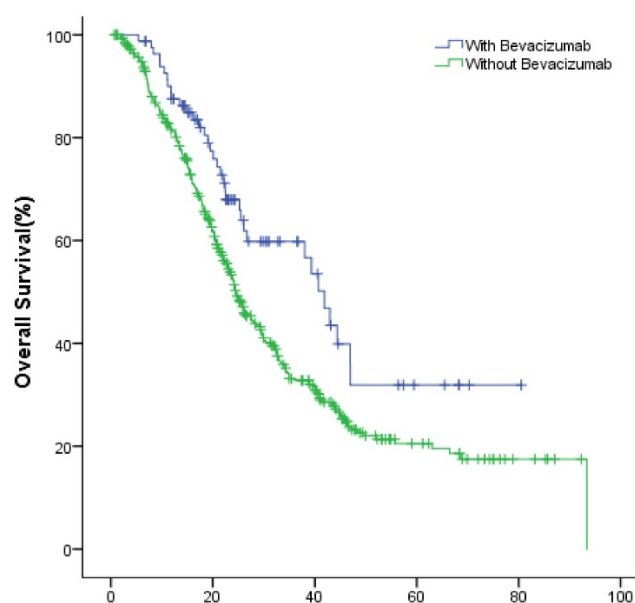


Figure 1: The OS of patients with or without bevacizumab.

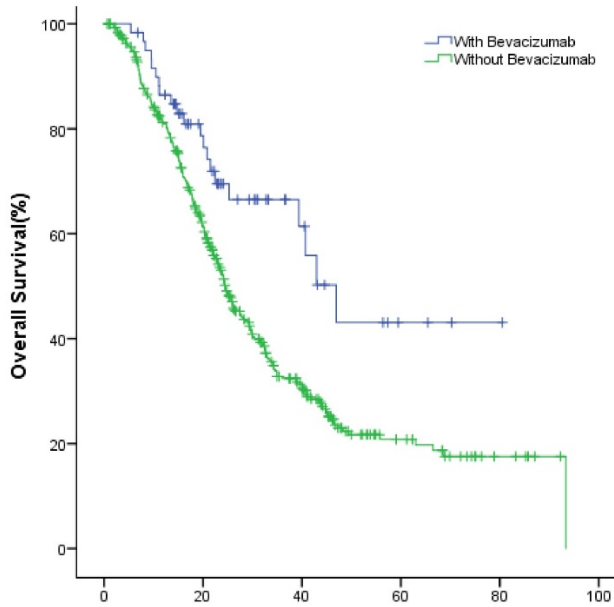


Figure 2: The OS of patients with and without bevacizumab in the first-line treatment.

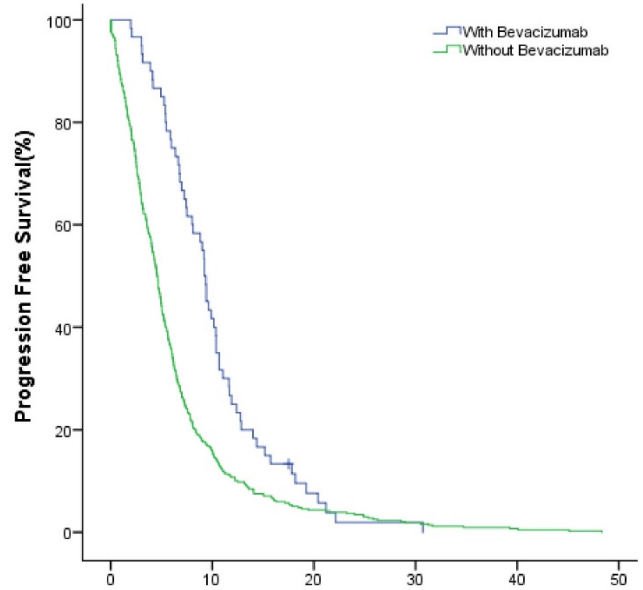


Figure 4: The PFS of patients with and without bevacizumab in the first-line treatment.

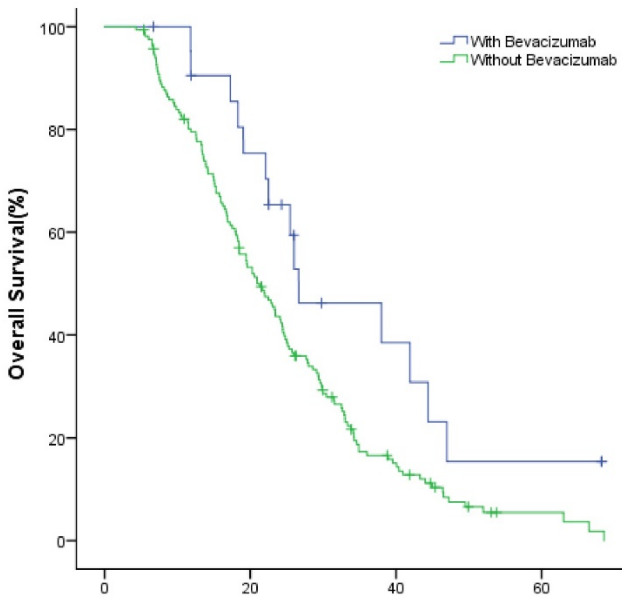


Figure 3: The OS of patients with and without bevacizumab in the second-line treatment.

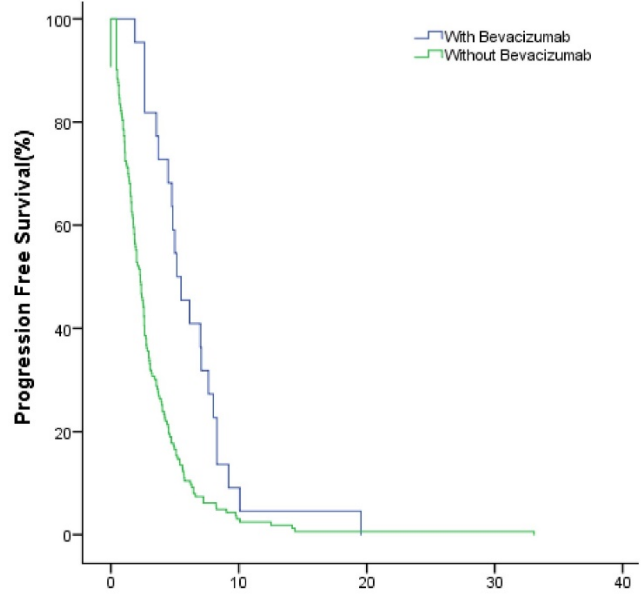


Figure 5: The PFS of patients with and without bevacizumab in the second-line treatment.

Discussion

The similar effect of bevacizumab in Caucasian mCRC patients and Chinese mCRC patients was indicated in clinical trials of AVF2017^[2] and ARTIST^[3]. However, In Chinese mCRC patients, the experiences of bevacizumab need accumulating. The early one-armed study of bevacizumab in Chinese mCRC patients found higher mortality and progressive rate (56.3% and 40.6%, respectively), which may relate to small patient sample. Later, both a recent study^[23] and our data^[22, 24, 25] showed that OS was significantly

prolonged after the administration of bevacizumab in mCRC, even in the later line^[14]. In addition, our studies also found that only patients received more than 4 cycles of bevacizumab can get survival benefit^[22] and bevacizumab benefit only refine to patients with initial LDH increase before treatment.

To our best knowledge, the current study was the first study to compare the effect of bevacizumab among different lines treatment when combined with chemotherapy in mCRC. It was shown that not only ORR and DCR but also OS and PFS were promising

after the addition of bevacizumab in each line treatment. In the entire group, the OS was prolonged indeed with the addition of bevacizumab when compared with patients without bevacizumab. Furthermore, both of OS and PFS were significant improved in bevacizumab group when compared with corresponding line chemotherapy alone groups. However, the OS were statistically insignificant among different line subgroups of bevacizumab group. All the patients in our study only received one line bevacizumab treatment since the patients received bevacizumab beyond its initial progression were excluded. Meanwhile, the current data, accordant with other studies, demonstrated that the combination of bevacizumab and standard chemotherapy really brought survival benefit to mCRC patients no matter it was added in the first- or the second-line treatment. The exact cause is unknown, but a similar finding was seen in non-small cell lung cancer(NSCLC) patients who were EGFR sensitive mutations and treated with tyrosine kinase inhibitors(TKIs)^[26]. Both clinical trials of IPASS and NEJSG002^[27, 28] were to investigate the sequence of gefitinib, the first generation of TKIs and chemotherapy in the first line and second line in patients with EGFR sensitive mutation. The OS were identical no matter the first- and second- line strategy was chemotherapy behind TKIs or the opposite, despite that the PFS of TKIs group was longer than chemotherapy in the first line. Therefore, the principle of TKIs administration was that it could be used in no matter which line. The reason of this phenomenon was unknown either in NSCLC patients as well.

Besides, the limits of this study should be taken into account before drawing a conclusion. Firstly, the retrospective data and small patients sample may cause bias. In addition, although this strategy were proven to be effective and be part of clinical practice already, the patients treated with bevacizumab beyond its initial progression were not covered in this study. The aim of excluding those patients was to guarantee the drug was received once in the patients of the study group during the whole course of treatment. As a consequence, it was possible to be compared with the patients in chemotherapy alone group. Moreover, only patients received more than four cycles of bevacizumab were recruited, since our previous study found the survival benefit refine to those group of mCRC patients.

In conclusion, once the patients received bevacizumab during the whole course of treatment, it really brought survival benefit to mCRC patients in no matter which line therapy. Nevertheless, the prospective and/or larger patients sample studies are urgently needed.

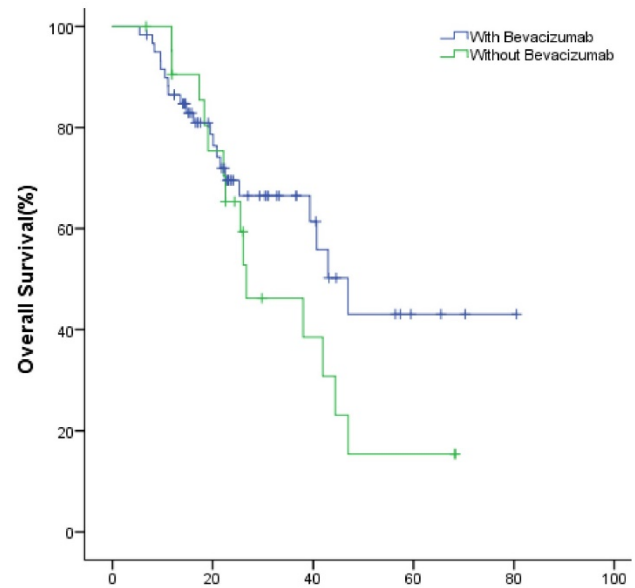


Figure 6: The OS of patients with bevacizumab in the first- and second-line treatment.

Acknowledges

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Competing Interests

The authors have declared that no competing interest exists.

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