

A Potential Administration-time Dependent Effect of Bevacizumab in Improving Overall Survival and Increasing Metastasis in Metastatic Colorectal Cancer

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Abstract

Background: The effectiveness of Bevacizumab has been demonstrated for the treatment of metastatic colorectal cancer. However, the minimum number of bevacizumab cycles needed to improve overall survival is unknown. In addition, anti-angiogenic treatment has been shown in preclinical studies to accelerate metastasis. To investigate these two issues, we performed a retrospective case-control study in Chinese patients with metastatic colorectal cancer.

Methods: Patients initially diagnosed as metastatic colorectal cancer at the Sun Yat-sen University Cancer Center from 2004 to 2010 were recruited. All patients treated with bevacizumab served as experimental group; patients not treated with bevacizumab were control group. The primary endpoints were overall survival and the incidence of new metastatic lesions in the liver and other organs.

Results: Patients received more than 4 cycles of bevacizumab showed a significantly prolonged overall survival than patients in the control group. The median overall survival was 31.53 months (95% CI, 23.22-39.85 months) and 19.70 months (95% CI, 16.61-22.79 months; $P=0.031$) for the experimental and control groups, respectively. The patients receiving bevacizumab more than 3 times showed an increased risk compared to the patients in control group of developing new metastatic lesions in the liver (17/23 versus 25/55, respectively, $P=0.022$) and other organs (14/23 versus 19/55, respectively, $P=0.032$).

Conclusion: More than 4 doses of bevacizumab were required to improve overall survival in metastatic colorectal cancer; a potentially accelerated metastasis rate was observed after more than 3 doses of bevacizumab. However, studies with larger patient sample sizes are urgently needed to validate our findings.

Keywords: Bevacizumab; Minimum duration; Accelerating metastasis; Colorectal cancer

Introduction

Angiogenesis plays a key role in the survival and invasion of cancer cells [1], thus making anti-angiogenesis a widely researched area of cancer care. Anti-angiogenesis therapy 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 [2]. Bevacizumab, the recombinant humanized monoclonal antibody to the vascular endothelial growth factor (VEGF) receptor, has been indicated for use for many types of cancer including advanced non-small cell lung cancer (NSCLC) [3,4], advanced renal cell carcinoma [5,6], metastatic colorectal cancer (mCRC) [7-12], and metastatic breast cancer [13,14], as its use can increase patient overall survival (OS) and progression-free survival (PFS).

Several clinical trials have demonstrated that bevacizumab prolongs OS or PFS [9-12] as a first or second-line therapy and in oxaliplatin-based or irinotecan-based regimens. In addition to phase III clinical trials, a large observational study, BEAT (Bevacizumab expanded Access Trial) [15], also demonstrated a prolonged OS with bevacizumab use. However, while bevacizumab and other anti-angiogenesis agents have shown effectiveness, there are still challenges associated with these agents. First, the optimal maximum dose and the minimum duration of bevacizumab treatment are still unknown. Bevacizumab treatment is often recommended for 6 months [16]; however, in the adjuvant setting, one year of bevacizumab administration was suspected to be

insufficient [17,18]. With regard to the lower dose limit, one preclinical study suggested that not only structural and functional effects but also antitumor activity can be induced by only one cycle of VEGF-specific inhibition [19]; however, no clinical data have revealed the minimum cycles required to extend OS. Another concern comes from the latest preclinical studies [20-22] indicating that anti-angiogenic treatments can accelerate metastasis. Paez-Ribes et al. [21] found that both a vascular endothelial growth factor receptor-2 (VEGFR2) inhibitor and an anti-angiogenic kinase inhibitor can induce not only increased invasiveness but also metastasis. Ebos et al. [20] reported a similar effect of a VEGF/platelet-derived growth factor receptor (PDGFR) kinase inhibitor under various conditions, including after intravenous injection of tumor cells or after the removal of primary orthotopically grown tumors. In addition, pretreatment of healthy mice with VEGF inhibitors prior to intravenous implantation of tumor

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cells also accelerates metastasis, known as “conditioned” tumor to be more aggressive [22]. To our knowledge, there is no published clinical evidence confirming this.

Given these unanswered questions, we performed a retrospective case-control study. We found that bevacizumab improved OS in patients with mCRC after the administration of more than four cycles and showed a potential to increase metastasis after three cycles.

Patients and Methods

Study population

All patients admitted to the Sun Yat-sen University Cancer Center from 2004 to 2010 with an Eastern Cooperative Oncology Group (ECOG) status ≤ 2 , a initial histological/pathological diagnosis of mCRC, and who had been treated with bevacizumab were selected as the experimental group. There were 43 patients in the experimental group. We randomly chose 1000 patients (the number was determined by a statistician as sufficient for a case-control study) who were diagnosed as colorectal cancer during the same time period at our hospital, among which 157 were initially diagnosed as mCRC. Those 157 patients served as control group.

The purpose of this study was two-fold. One objective was to survey patient response to bevacizumab and the minimum duration required in order to improve OS, and the other goal was to explore whether bevacizumab influences metastasis and the potentially correlated administration cycles. To achieve these goals, the OS were studied. Available CT scans were also analyzed, and newly involved organs were recorded; in particular, new lesions in the liver were recorded, as liver is the most common organ involved by colorectal cancer.

Treatment regimen

5 and 6 patients had been treated with bevacizumab (5 mg/kg, every two weeks) in conjunction with an oxaliplatin-based regimen as a first and second-line chemotherapy, respectively, while 8 and 10 patients were treated with a bevacizumab plus irinotecan-based regimen as first-line and second-line chemotherapy, respectively. The combined chemotherapy agents for the 14 patients who received bevacizumab as a third-line therapy were FOLFOX (4 patients), FOLFIRI (3 patients), FOLFIRINOX (2 patients), irinotecan (3 patients), and S-1 (2 patients). The number of cycles of bevacizumab that were administered varied from 1 to 27; 19 patients received between 1 and 4 cycles, 18 patients received between 5 and 12 cycles, and 6 patients received more than 12 cycles.

Statistical analyses

Patient OS was the primary statistical endpoint of the study, and it was calculated from diagnosis until death or the date of last follow-up (August 31st, 2011). The OS was analyzed using the Kaplan-Meier method, which included calculations of medians and survival curves. The Chi-squared test was used to compare factors that might influence OS, while the incidence of newly developed metastatic lesions and the analysis of factors that might influence the number of new lesions were analyzed by the Chi-squared or Wilcoxon test. A *P* value less than 0.05 was considered statistically significant. All statistical analyses were conducted using the SPSS 13.0 software package.

Results

Patient characteristics

Patient characteristics of both groups are shown in Table 1. The

last follow-up was conducted on August 31st, 2011 through a telephone interview. At that time, thirty-eight patients in the experimental group were dead, four patients were lost to follow up, and one patient was living. In contrast, one hundred and seventeen patients in the control group were dead, twenty-two patients were lost to follow up, and eighteen patients were living.

Bevacizumab did not improve OS for all patients in the experimental group

Among the patients in the experimental group, no patients achieved a complete response (0%). A partial response was recorded in 11 patients (25.58%), stable disease was recorded in 10 patients (23.26%), progressed disease was recorded in 8 patients (18.60%), and 14 patients were recorded as not available (32.56%). The OS for the experimental and control groups were 29.20 months (95% confidence interval [95% CI], 22.53-35.87 months) and 19.70 months (95% CI,

Patient characteristics	Experimental group		Control group	P	
	All patients	Patients who received bevacizumab more than 4 times		(1) ^b	(2) ^c
Number	43	24	157		
Gender				0.602	0.268
Male	25	12	98		
Female	18	12	59		
Age (years)				0.475	0.958
Median (range)	55(35-81)	56(35-81)	54(13-80)		
≤ 60	30	15	99		
> 60	13	9	58		
ECOG				0.917	0.379
0	14	10	46		
1	28	14	107		
2	1	0	4		
Primary tumor				0.589	0.648
Colon	30	17	100		
Rectum	13	7	57		
No. of metastatic organs at initial diagnosis				0.060	0.055
1	34	20	94		
2	7	4	43		
≥ 2	2	0	20		
Site of metastases at initial diagnosis					
liver	40	21	140	0.576	0.733
lung	9	3	45	0.340	0.135
History of treatment	43	24	157		
Palliative surgery	7	5	20	0.615	0.337
Interventional therapy	13	9	48	0.966	0.319
Cetuximab exposure	13	3	29	0.137	0.578
Chemotherapy lines ^a				<0.001	0.013
First line	43	24	157		
Second line	32	16	60		

a: only the first line and second line were compared; b: All patients in the experimental group vs. the control group; c: patients who were treated with bevacizumab more than 4 times in the experimental group vs. the control group

Table 1: Patient baseline characteristics in the experimental group and the control group.

16.61-22.79 months), respectively ($P=0.152$). The Kaplan-Meier curves are shown in Figure 1. There was no significant difference between the two groups.

Bevacizumab did improve OS for patients who were treated with bevacizumab more than 4 times

Among the 43 patients in the experimental group, some received the agent very few times. Some patients received bevacizumab one to three times during the cytotoxic regimen and then halted use while continuing chemotherapy. The discontinuations were not due to either tumor progression or serious adverse events. Possible explanations are that patients could not afford bevacizumab or had difficulty obtaining it, as bevacizumab was only available in Hong Kong or foreign countries before 2010 when it was approved by the Chinese State Food and Drug Administration. Given these situations, we had an opportunity to examine the patients who gained a benefit from bevacizumab and determine how many cycles they had received.

It was found that the patients who received bevacizumab more than four times obtained a prolonged OS of 31.53 months (95% CI, 23.22-39.85 months), which is significantly longer than that observed in the control group (19.70 months [95% CI, 16.61-22.79 months]; $P=0.031$). The Kaplan-Meier curves are shown in Figure 2. To exclude the possibility that the prolonged OS was a result of coincidence, we compared the OS between patients who were exposed to bevacizumab more than 5 times and the control group and found that the OS was 35.00 months (95% CI, 24.44-45.57 months) and 19.70 months (95% CI, 16.61-22.79 months; $P=0.026$), respectively. A significant result was also observed in patients who received bevacizumab more than 6 times.

Bevacizumab had a potential to increase metastasis

Among the 43 patients who had been administered bevacizumab, 29 had a CT scan in our hospital, while 55 of the 157 patients in the control group had a CT scan available, as shown in Table 2. Any new lesions in the liver or other organs were recorded and compared between the two groups. 23 patients experienced new lesions after the discontinuation of bevacizumab.

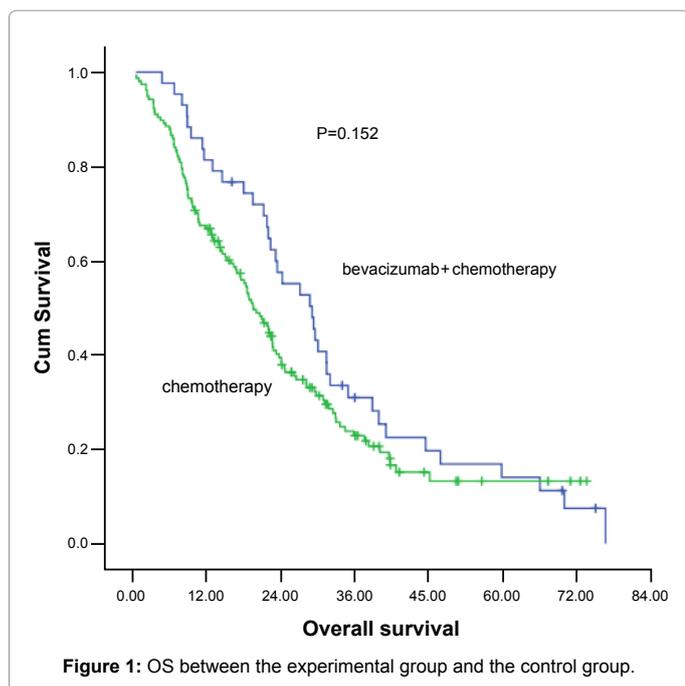


Figure 1: OS between the experimental group and the control group.

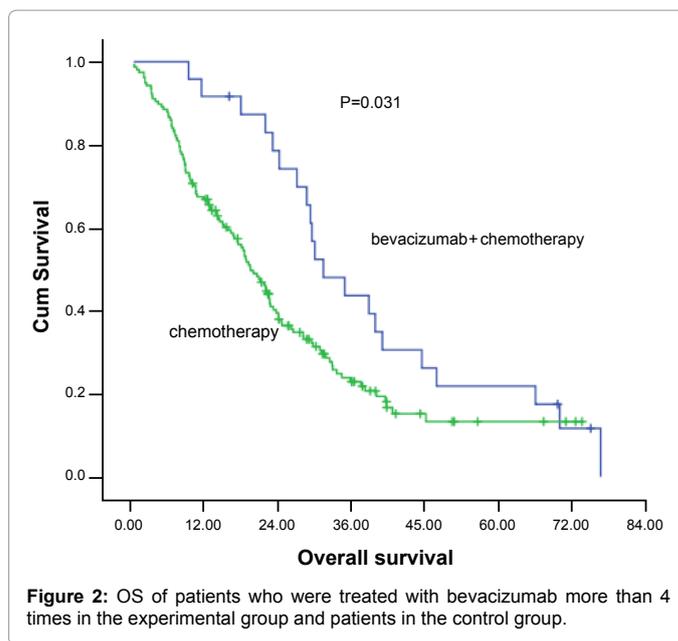


Figure 2: OS of patients who were treated with bevacizumab more than 4 times in the experimental group and patients in the control group.

There was no significant difference in the incidence of new metastases between the groups; new metastatic lesions in the liver were found in 18/29 patients in the experimental group versus 25/55 patients in the control group ($P=0.148$), and newly involved organs were found in 15/29 patients in the experimental group versus 19/55 patients in the control group ($P=0.127$), as shown in table 2. Similar to the evaluation of the impact of bevacizumab on OS, there were patients who received the agent only one or two times. We found that the incidence of new metastases in the patients who used the agent more than three times differed significantly from the patients in the control group. New metastatic liver lesions were found in 17/23 in the experimental group patients versus 25/55 in the control group patients ($P=0.022$) and newly involved organs were found in 14/23 in the experimental group patients versus 19/55 in the control group patients ($P=0.032$), as shown in Table 2. Other possible factors that may affect metastases are presented in Table 2. A significant difference also existed when patients used the agent more than 4 times.

Discussion

Both the AVF2107g trial [7] and the ARTIST trial [8] revealed that addition of bevacizumab to the first-line therapy improved OS. However, the limitation of the two trials is that they adopted IFL/mIFL as the chemotherapy regimen combined with bevacizumab, and this regimen was less effective than FOLFIRI [9]. To overcome this limitation, Fuchs et al. [9] conducted a clinical trial in which FOLFIRI combined with bevacizumab as a first-line therapy was shown to increase OS. However, as a first-line therapy, bevacizumab failed to improve OS when combined with FOLFOX/XELOX [11]. Based on the all of the randomized clinical trials involving both oxaliplatin and irinotecan-based regimens, a meta-analysis [23] was conducted with the aim of minimizing the heterogeneity of the studies. This meta-analysis revealed that bevacizumab truly improved OS in patients with mCRC. The ability of bevacizumab to improve OS in Chinese patients with mCRC was supported by our study and has also been fully demonstrated in the randomized phase III clinical trial, ARTIST [8]. More importantly, we found that OS was significantly improved when bevacizumab was given more than 4 times; the exclusion of

Patient characteristics	Experimental group (all patients)	Experimental group (more than 3 times bevacizumab)	Control group	P	
				(1) ^c	(2) ^d
Number	29	23	55		
Gender				0.105	0.304
Male	14	12	37		
Female	15	11	18		
Age (years)				0.628	0.788
Median (range)	55(31~81)	57(31~81)	51(13~80)		
≤60	19	15	39		
>60	10	8	16		
Primary tumor				0.240	0.447
Colon	21	16	32		
Rectum	8	7	23		
No. of metastatic organs ^a				0.798	0.895
1	15	12	29		
2	8	6	12		
≥3	6	5	14		
No. of metastatic lesions in liver ^a				0.124	0.106
0	2	1	16		
1	9	7	15		
2	4	3	5		
≥3	14	12	19		
Duration between imaging studies (weeks) ^b	49.20 ± 35.49	66.83 ± 31.88	58.34 ± 44.62	0.821	0.060
Frequency of imaging study	6.6 ± 2.59	6.8 ± 2.57	6.4 ± 2.43	0.429	0.231
The time of first CT scan performed ^{a,b}				0.287	0.472
First detection	6	5	10		
During first-line chemotherapy	21	16	34		
During second-line chemotherapy	2	2	11		
Span from diagnosis to the first imaging study (weeks) ^b	32.11 ± 46.08	27.74 ± 38.81	18.10 ± 32.85	0.104	0.279
Incidence of new emerging metastatic lesion(s)					
New lesions in liver	18	17	25	0.148	0.022
New organs involved	15	14	19	0.127	0.032

a: at the first time of available CT scan; b: data are presented as the mean ± standard deviation; c: all patients in the experimental group vs. the control group; d: patients who were treated with bevacizumab more than 3 times in the experimental group vs. the control group

Table 2: Patient characteristics and different potential risks of metastasis in the experimental group and the control group whose CT scans were available.

patients receiving less than 4 treatments of bevacizumab increased the reliability of our findings. We continued to screen the number of cycles with the purpose of eliminating coincidence and found that the OS benefit persists if patients received bevacizumab more than 5 or 6 times. In addition, to clarify that the OS advantage of bevacizumab was not caused by an increased number of patients in the experimental group receiving second-line chemotherapy ($P=0.013$), we re-analyzed the data using patients in the control group who received first and second-line chemotherapy, and the results were the same (OS benefit and four times of bevacizumab needed, data not shown).

Based on the available CT scans, we found that, after treatment with bevacizumab, more patients experienced new lesions than their bevacizumab-free counterparts did in a given time period. To exclude potential influences from other factors associated with new metastases, we focused on two aspects. The first aspect considered was the tumor burden, involving the number of organs with cancer and the metastatic lesions in the liver based on the first CT scan. Since chest and abdominal CT scans were monitored during follow up in our cancer center, the organs which were focused on were lung, liver, spleen and vertebrae included in the scan. Between the two factors, the new metastatic lesions in the liver were more important because the liver is the most frequent organ involved in CRC, and liver review is required in each follow up. Both factors were balanceable in the two

groups, and the clinical stage (which also reflects the tumor burden) was taken into account as all patients were initially diagnosed at Dukes' D. The second aspect was the monitoring time, since as the follow-up time increase, the possibility to develop new metastases also increase. To clarify this, the span of the imaging studies were compared between study group and control group; so were the duration from diagnosis to the first imaging study. No significant difference was found between the two groups. To our knowledge, our result provides the first clinical evidence to support the idea that bevacizumab accelerates metastasis.

In the C08 clinical trial [17], which investigated the role of bevacizumab in adjuvant chemotherapy in early stage CRC, the DFS no longer differed after three years of follow up, perhaps indicating that the metastasis rate was irrespective of bevacizumab or that bevacizumab should be administered for a longer time. However, a majority of patients in the adjuvant setting was without residual cancer cells, but each patient in our study had a visible tumor burden from the time of diagnosis. The potential risk of accelerating metastasis appears to contradict the daily clinical practice that bevacizumab can improve OS, but these data agree with the results from three previous preclinical studies [20-22], though its actual mechanism is unknown. We hypothesize that the pruning of vessels and the inability of bevacizumab to reduce permeability [2] results in bevacizumab aggravating hypoxia rather than relieving it. This state of hypoxia may

induce a more aggressive tumor cell type and accelerate metastasis. One theory is that there are at least five types of vessels associated with cancer [1,24]. Anti-VEGF drug can effectively block the early forming mother vessels while late-forming vascular malformations are largely resistant to this type of agent. This finding offers a possible explanation for the limited effectiveness of an anti-VEGF-A/VEGFR treatment of human cancers, which are typically present for months to years before discovery and are largely populated by late-forming blood vessels. This finding may also be an explanation for the accelerated metastasis found in our study. We also screened the data to determine that the accelerated metastasis occurred after bevacizumab was administered more than 4 times to exclude a coincidence.

There are several limitations in our study. First, bevacizumab was not approved by the Chinese State Food and Drug Administration until 2010, which caused the total number of patients in our study to be limited, as very few patients could access the agent from markets outside the Chinese mainland. Second, our study was retrospective. All information was based on medical records, which may not be complete. Third, the new lesions in the liver and other organs may not reflect all newly developed metastases, as there may be new lesions occurring in organs other than these. Fourth, we only have CT scan results for the period of the patients' whole treatment, which does not represent the entire span of the disease.

In summary, we conducted a retrospective study indicating that bevacizumab had a favorable impact on OS while having an adverse potential impact on metastasis, both of which depended on usage time. However, a study with larger patient numbers and clinical trials with appropriate designs are urgently needed to validate the findings in our study.

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