

ORIGINAL ARTICLE

Efficacy and adverse reactions of combination therapy of bevacizumab and 5-fluorouracil in patients with metastatic colon cancer

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Summary

Purpose: To observe the efficacy and side effects of combined treatment of bevacizumab and 5-fluorouracil in patients with metastatic colon cancer.

Methods: Sixty patients with histopathologically confirmed metastatic colon cancer were treated with bevacizumab and 5-fluorouracil (the study group) or 5-fluorouracil alone (the control group). 400 mg/m² 5-fluorouracil was given intravenously and maintained by a micropump (2400 mg/m²) for 46 hrs. A treatment cycle consisted of 14 days. All patients received at least 4 cycles of treatment. Serum vascular endothelial growth factor (VEGF) concentrations in colon cancer patients of the two groups were evaluated before and after chemotherapy. The short-term treatment efficacy was assessed and followed every 3 months for survival analysis, while adverse reactions were also observed and recorded.

Results: Before the treatment, no differences were observed in VEGF levels between the two groups. However, after 4 cycles of chemotherapy, VEGF level in the study group was

markedly lower vs the pretreatment level. No difference was observed in VEGF level in the control group after treatment. The effective rate in the two groups after treatment was response rate (RR)=86.7% and 53.3%, respectively ($p<0.05$). A 24-month follow-up showed that the median progression-free survival (PFS) of the study group was 9.87 months and the median survival 16.9 months. The median PFS of the control group decreased to 6.75 months with median survival of 12.45 months. Data analysis showed significant differences in PFS and median overall survival (OS) between the two groups ($p<0.05$). Besides, no difference was observed in the adverse reactions between the two groups during treatment (all $p>0.05$).

Conclusions: Combined treatment of bevacizumab and 5-fluorouracil can reduce the serum VEGF level of patients with metastatic colon cancer and prolong their PFS and OS.

Key words: bevacizumab, colon cancer, efficacy, 5-fluorouracil, survival

Introduction

Colon cancer is one of the most common malignant tumors in the world. It refers to a malignant transformation of colonic mucosal epithelial cells that is induced by various pathogenic factors. About one million people are diagnosed with colon cancer each year, especially in developed countries such as North America and Western Europe [1,2].

More than 50% of colon cancer patients die of disease, and the mortality rate ranks 4th among cancers [3]. Its high incidence is related to heredity, colon adenoma, colon polyposis, chronic inflammatory disease, less fiber, high-fat diet as well as lack of physical activity. The onset of colon cancer is characterized with vague clinical manifestations

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Received: 23/08/2018; Accepted: 28/09/2018

in the early stage and slow progression. Most of the cases are already metastatic when diagnosed. Reports have shown that patients with metastatic colon cancer have lower quality of life and no more than 5% 5-year survival rate [4]. Also, the incidence rate is increasing with age [5,6].

Bevacizumab (Avastin) is a recombinant humanized VEGF monoclonal antibody that directly inhibits the binding and activation of VEGF and its receptor, which exerts anti-angiogenic and anti-tumor activity [7-9]. In 2010 FDA approved bevacizumab for first-line treatment of advanced colon cancer patients [10]. Hurwitz et al. [11] reported a phase III clinical trial of bevacizumab combined with chemotherapy for treatment of metastatic colon cancer, which extended the OS of unresectable patients compared to chemotherapy alone. According to the analysis of this clinical trial, the addition of bevacizumab-targeted-therapy to chemotherapy extended the median survival from 14.6 months to 17.9 months, which confirmed that this combination could improve the treatment efficiency and prolong the OS and PFS of patients. To date, bevacizumab has been widely used in the first-line treatment of metastatic renal cell carcinoma and advanced NSCLC and has also achieved encouraging results in the application to other malignant tumors such as liver cancer, gastric cancer and colon cancer [12-14]. Bevacizumab has a milder adverse effect profile compared with chemotherapy and its general combination with chemotherapy does not increase toxic side effects. Common side effects of bevacizumab administration include proteinuria, hypertension, hemorrhage, thrombosis which are generally mild, moderate and mostly clinically controllable, and the potentially life-threatening gastrointestinal hemorrhage [15,16]. In this research, we investigated the efficacy of bevacizumab combined with 5-fluorouracil in treating advanced colon cancer patients.

Methods

Research subjects

Sixty patients with metastatic colon cancer who were treated from January 2015 to January 2016 in our hospital were included in this study. All cases were histopathologically confirmed as adenocarcinoma and were not treated with chemotherapy and bevacizumab before, or their treatment interval was more than half a year. This study was approved by the ethics committee of the Affiliated Hospital of Jiangnan University. Signed written informed consents were obtained from all participants before the study entry.

Inclusion criteria

1) Primary lesions and metastatic lesions of colon cancer were confirmed by pathology as adenocarcinoma; 2) Physical status: ECOG performance status 0-2; 3) Objectively evaluable tumor lesions; 4) No history of other malignant tumors; 5) Normal coagulation and routine urine tests; 6) No history of hypertension, or hypertension with drug control systolic blood pressure <140 mmHg, diastolic blood pressure <90 mmHg; 7) Normal blood, heart, liver and kidney function, with no apparent chemotherapy contraindications.

All patients signed the relevant informed consent form for chemotherapy.

Exclusion criteria

1) Those who had mental abnormalities and cannot express subjective wishes or symptoms; 2) Physical status: ECOG performance status ≥ 3 ; 3) Primary lesions or metastatic lesions of colon cancer not confirmed by pathology; 4) Coagulation abnormalities or urine routine tests for positive urinary protein; 5) Those who had severe uncontrolled medical disease or acute infection and cannot tolerate chemotherapy; 6) Pregnant or lactating women.

Treatment plan and grouping

1) Patients in the study group were treated with bevacizumab plus 5-fluorouracil: bevacizumab 5 mg/kg; 400 mg/m² 5-fluorouracil was given intravenously and maintained by a micropump (2400 mg/m²) for 46 hrs. A

Table 1. Solid tumors evaluation criteria (RECIST)

Therapeutic response	Specific standard
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. New lesion(s) signify PD.

treatment cycle consisted of 14 days. 2) Patients in the control group were treated with 5-fluorouracil alone. A treatment cycle consisted of 14 days. All patients received at least 4 cycles of treatment.

Fasting venous blood in the two groups of patients was taken before and after chemotherapy, and ELISA assay detected the concentration of VEGF.

Efficacy evaluation

According to the World Health Organization (WHO) solid tumor efficacy evaluation criteria (Table 1), the ef-

ficacy was evaluated after 4 cycles of chemotherapy, including the advanced-stage complete remission (CR), partial remission (PR), disease stabilization (SD) and disease progression (PD). Among them CR+PR were considered effective while CR+PR+SD were considered as clinical disease control.

Survival rate and adverse reactions

The progression or death of tumor was detected by follow up from the beginning of chemotherapy to the reexamination. The patients in the two groups were fol-

Table 2. General comparison of general characteristics of the two groups of patients

Characteristics	Control group	Study group	<i>p</i>
Age (years)			0.389
≤60	10	8	
>60	20	22	
Gender			0.300
Male	19	16	
Female	11	14	
VEGF	422.5±39.4	418.1±32.4	0.578
Differentiation			0.389
Poor	8	10	
Well/moderate	22	20	

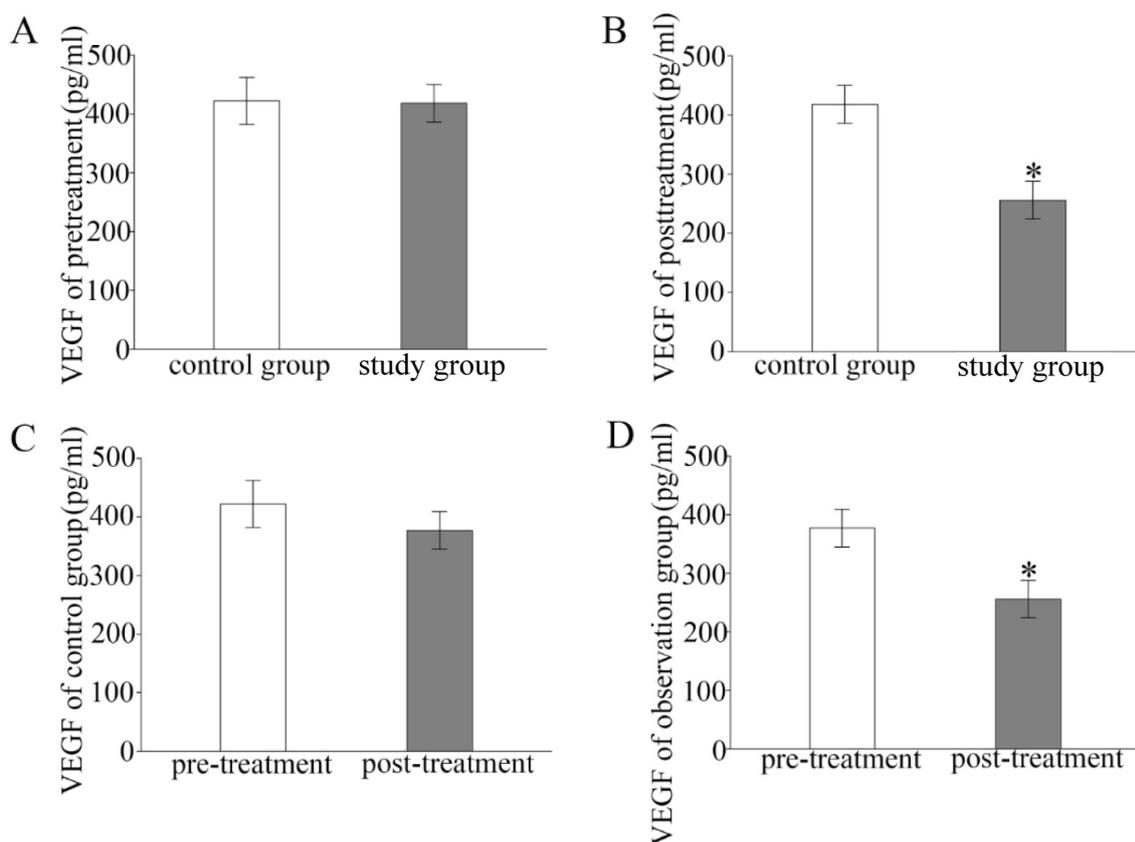


Figure 1. Changes in serum VEGF levels before and after chemotherapy in the two groups of patients. **A:** Comparison of serum VEGF levels before treatment between two groups. **B:** Comparison of serum VEGF levels after treatment between two groups. **C:** Comparison of serum VEGF levels before and after treatment in patients in the control group. **D:** Comparison of serum VEGF levels before and after treatment in patients in the study group. **p*<0.05.

lowed up to January 2018. PFS and overall survival were calculated. Besides, the gastrointestinal tract and side effects such as myelosuppression, allergic reactions, liver/kidney dysfunction and neurotoxicity were observed and recorded.

Statistics

SPSS 17.0 software (SPSS Inc., Chicago, IL, USA) was used for data analyses and results were expressed as $\bar{x} \pm s$. T-test was performed to analyze the quantitative data. The percentage data assessed with χ^2 test. Survival was analyzed and plotted using the Kaplan-Meier method and Log Rank test was used to compare significant differences between groups. A p value < 0.05 was considered statistically significant.

Results

Clinical data of patients in the two groups

Of 60 patients with metastatic colon cancer from January 2015 to January 2016, 35 (58.3%) were male and 25 (41.7%) female. Their age ranged from 35 to 79 years, with 42 (70.0%) cases more

than 60 years and 18 (30.0%) cases less than 60 years. Forty two cases (70%) had moderate tumor differentiation and 18 (30%) had poor differentiation. No significant differences existed in the general data parameters (Table 2).

Serum VEGF levels before and after treatment

Before treatment, no difference existed in serum VEGF levels between the two groups (Figure 1A). After the treatment, the serum VEGF levels in the study group were markedly reduced (Figure 1B). Meanwhile, after 30 cycles of bevacizumab plus 5-fluorouracil regimen, VEGF levels in the the study group patients decreased significantly ($p < 0.05$) (Figure 1C). In contrast, no difference was observed in VEGF levels of patients in the control group who were treated with 5-fluorouracil alone for 4 cycles (Figure 1D).

Comparison of clinical effects between the two groups

Sixty colon cancer patients were evaluated by RECIST 1.1 before and after treatment. The effec-

Table 3. Comparison of clinical effects between the two groups

Group	Control group n	Study group n	p
CR	2	4	0.335
PR	5	12	0.042
SD	9	10	0.50
PD	14	4	0.005
CR+PR	7	16	0.016

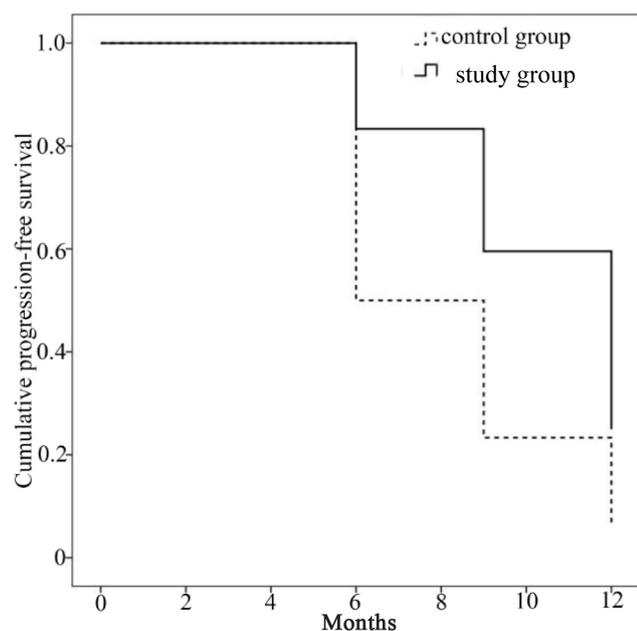


Figure 2. Comparison of progression-free survival between the two groups ($p < 0.05$).

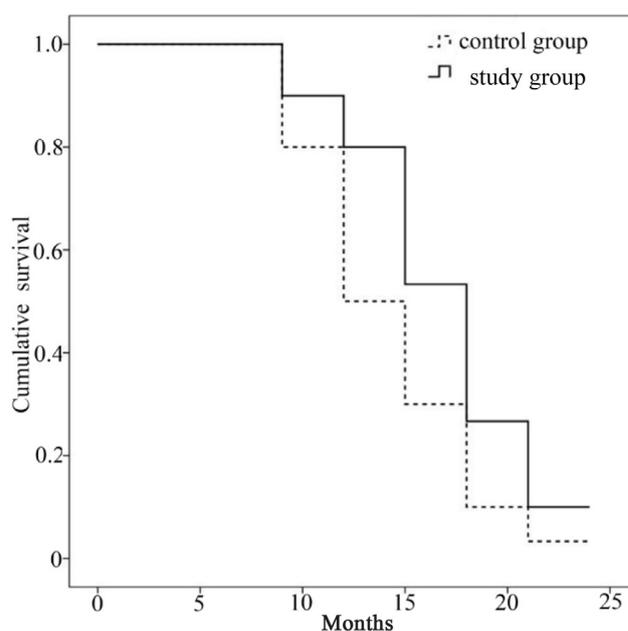


Figure 3. Comparison of overall survival between the two groups of patients ($p < 0.05$).

Table 4. Adverse reactions of the two groups

Adverse reactions	Control group n	Study group n	p
Neurotoxicity	1	0	0.50
Vomit	6	7	0.50
Diarrhea	13	12	0.50
Leukopenia	3	5	0.353
Thrombocytopenia	1	2	0.50
Rash	7	9	0.386

tive rate of RR was 86.7% and 53.3% in the study and control groups. Statistical analysis indicated that treatment of bevacizumab in combination with 5-fluorouracil was more effective than 5-fluorouracil alone ($p < 0.05$) (Table 3).

Comparison of progression-free survival between the two groups

A 24-month follow-up showed that the median PFS was 9.87 months in the study group (95% CI: 8.581-10.919) and 6.75 months (95% CI: 6.566-7.434) in the control group ($p < 0.05$; Figure 2).

Comparison of long-term efficacy between two groups

The median OS was 12.45 months (95% CI: 11.41-13.23) in the control group and 16.9 months (95% CI: 16.2 -17.8) in the study group ($p < 0.05$). The 2-year OS rates of the study group and the control group were 25.48% and 9.68%, respectively ($p < 0.05$; Figure 3).

Adverse reactions

In the course of treatment, the adverse reactions in the two groups included leukopenia, thrombocytopenia, digestive tract reactions and neurotoxicity. No side effects such as hemorrhage, thrombosis and proteinuria were observed. There was no difference between the two groups regarding adverse reactions (all $p > 0.05$) (Table 4).

Discussion

Colon cancer is one of the most common malignant tumors of the digestive tract. The incidence rate of colon cancer has been increasing year by year. In the United States, about 20% of colon cancers are associated with familial clustering [17]. About 25% of patients with colon cancer have metastases at initial diagnosis, while about 50% develop metastasis in the course of disease. Metastatic colon cancer is a leading cause of death reflecting its high malignant behavior [18,19].

VEGF plays a vital role in hematogeneous and nodal metastasis [20,21]. Some studies have shown that high VEGF levels in colon cancer patients suggest late stage of disease or distant metastasis. Besides, serum VEGF levels are decreased after systemic chemotherapy, suggesting that they can help predict chemotherapy efficacy and can be useful as an essential indicator for recurrence and metastasis of colon cancer [22,23].

Bevacizumab is a recombinant humanized monoclonal antibody that plays a crucial role in anti-tumor angiogenesis by directly blocking the binding and activation of VEGF to its receptor [24]. Bevacizumab, the anti-VEGF targeting drug, is currently used in the treatment of colon cancer, NSCLC and glioma, and has achieved good results. *In vivo* and *in vitro* detection systems have confirmed that IgG1 antibody binds to the human VEGF and blocks its biological activity. Bevacizumab can bind to VEGF receptor and prevent it from binding with receptors on the cell surface. In an *in vitro* angiogenesis model, VEGF was bound to its corresponding receptor, leading to endothelial cell proliferation and neovascularization [25,26]. Studies have shown that bevacizumab combined with chemotherapy as first-line treatment of colon cancer can significantly benefit patients compared with chemotherapy alone [27-29]. Moreover, this combined therapy of bevacizumab and chemotherapy can also improve the resection rate of patients who were initially considered as losing the chance of surgical resection [30].

In this study, we selected 60 patients with metastatic colon cancer. Among them, 30 patients received 5-fluorouracil in combination with bevacizumab targeted therapy. The results demonstrated that the VEGF level decreased in most of the 60 subjects after 4 cycles of treatment. Moreover, especially in the study group, serum VEGF levels decreased significantly after 4 cycles of bevacizumab plus 5-fluorouracil. However, serum VEGF levels in the control group did not show significant decrease after treatment. Besides, the efficacy of treatment was found to be RR=86.7% in the study group and

RR=53.3% in the control group, indicating that the effective rate of the study group using bevacizumab combined with chemotherapy was markedly higher than that using chemotherapy alone. Hurwitz et al. [11] explored the efficacy of bevacizumab with chemotherapy in a phase III clinical trial and found that the effective rate of patients receiving bevacizumab along with chemotherapy was 44.8%, while that of patients receiving placebo combined with chemotherapy was only 34.8% ($p < 0.05$) [11].

In the evaluation of therapeutic efficacy, our study was consistent with literature reports. Besides, we also found that the decreasing rate of VEGF after bevacizumab was higher, which also indicated that bevacizumab could reduce the serum VEGF level of patients and improve the therapeutic effect. This finding also suggested that the decrease of VEGF level in patients with metastatic colon cancer correlated with the efficacy of chemotherapy. Furthermore, the median overall survival time of the study group was longer compared with the control group, which was consistent with results reported before [23]. As for the adverse reactions,

the combination treatment of bevacizumab and chemotherapy in metastatic colon cancer patients did not increase significantly the side effects.

Conclusions

Bevacizumab in combination with 5-fluorouracil can reduce the serum VEGF level of patients with metastatic colon cancer and prolong the patient PFS and OS.

Acknowledgements

This study was supported by National Natural Science Foundation of China (81772636); Jiangsu Provincial Medical Youth Talent (QNRC2016162); Research Project of Health and Family Planning Commission Wuxi City (Q2017518); and Wuxi Young Medical Talents (QNRC063).

Conflict of interests

The authors declare no conflict of interests.

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