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Efficacy and safety of bevacizumab combined with chemotherapy in the treatment of advanced colorectal cancer and the effect on its adverse reactions

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Abstract: To evaluate the efficacy and safety of bevacizumab combined with chemotherapy in the treatment of advanced colorectal cancer and the effect on its adverse reactions, 100 patients with advanced colorectal cancer admitted to our hospital from March 2019 to March 2021 were identified as study subjects and were randomly divided into a control group and an experimental group, with 50 cases in each group. The control group was treated with chemotherapy, and the experimental group was given a combination of bevacizumab with chemotherapy. The treatment efficacy, safety, and incidence of adverse reactions in both groups were analyzed and compared. The effectiveness and disease control rate of the experimental group were 50% and 96%, which were significantly higher than those of 26% and 80% in the control group ($P<0.05$). After treatment, the experimental group exhibited a significantly lower serum vascular endothelial growth factor level and heat shock protein 90α (HSP90α) level compared with that of the control group ($P<0.05$). Markedly higher apoptosis index of tumor cells was observed in the experimental group than in the control group ($P<0.05$). The incidence of adverse reactions was 8% in the experimental group, which was significantly lower than that of 28% in the control group ($P<0.05$). The post-treatment quality of life scores in the experimental group exceeded that in the control group ($P<0.05$). Bevacizumab combined with chemotherapy for advanced colorectal cancer boosts treatment efficiency, promotes apoptosis of tumor cells, down regulates HSP90α level and enhances patients' quality of life with high safety, which is worthy of clinical promotion and application.

Keywords: Bevacizumab, chemotherapy, advanced colorectal cancer, efficacy, safety.

INTRODUCTION

Colorectal cancer refers to cancers of the colorectal epithelium, such as colon and rectal cancers, with adenocarcinoma frequently seen in most cases and squamous carcinoma in a few (Formica *et al*., 2021). As indicated by relevant data (Snyder *et al*., 2021), colorectal cancer is the third most common malignancy with a mortality ranking sixth of all malignancies. Notwithstanding a poorly understood etiology, its onset is reported to relate to the environment, dietary habits, and genetic factors (Svaton *et al*., 2021). The non-specific early symptoms usually lead to a belated diagnosis when the disease has progressed to a middle or advanced stage and an inferior treatment efficiency (Pena-Cabia *et al*., 2021). Colorectal cancer is characterized by clinical manifestations such as blood in stool and changes in bowel habits and stool characteristics, with a high mortality rate, which seriously threatens people's health and life safety (Higashijima *et al*., 2021). Chemotherapy is the common treatment for advanced colorectal cancer in clinical practice, which, however, has been reported with unsatisfactory therapeutic efficacy in stand-out treatment. With the in-depth research on molecular mechanisms of tumors, targeted drugs targeting tumor molecular markers and signaling pathways have captured greater academic attention (Chen JC *et al*., 2021; Yoshida *et al*., 2021). Vascular endothelial growth factors can act on vascular endothelial cells by binding specifically to the corresponding receptors to promote angiogenesis. Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) and affects vascular permeability and proliferation as well as endothelial cell migration and survival to achieve inhibition of tumor angiogenesis, growth, and metastasis (Aoshima *et al*., 2021; Leslie *et al*., 2021). It has been reported that the combination of bevacizumab and chemotherapeutic drugs improved the therapeutic effect and enhanced the penetration of chemotherapeutic drugs inside the tumor (Shukla *et al*., 2021). Accordingly, this study was conducted to analyze the efficacy and safety of bevacizumab in combination with chemotherapy for advanced colorectal cancer and the effect on adverse effects. It is reported as follows.

MATERIALS AND METHODS

General information

One hundred cases of advanced colorectal cancer patients admitted to our hospital from March 2019 to March 2021 were selected as research subjects, and were randomly divided into the control group and the experimental group,

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with 50 cases in each group.

Inclusion and exclusion criteria

Inclusion criteria: ① Patients who were diagnosed with advanced colorectal cancer by computed technology (CT) or magnetic resonance imaging (MRI), fiberoptic colonoscopy, and biopsy; ② Patients with an Eastern Cooperative Oncology Group physical status score (ECOG) (Powles *et al*., 2021) of 0-2 points; ③ Patients who were treated with bevacizumab for at least 2 cycles and had imaging evaluations; ④ This study was approved by the hospital ethics committee, and patients and their families were aware of the purpose of this experimental study and signed an informed consent form. Exclusion criteria: ① Patients with cardiac, hepatic, and renal dysfunction; ② Patients with allergies to the drugs used in this study; ③ Patients with severe mental illness.

Methods

The control group was treated with chemotherapy using the XELOX chemotherapy regimen, with oxaliplatin (manufacturer: Jiangsu Hengrui Pharmaceutical Co., Ltd.; State Drug Standard: H20050962; specification: 100ml: 0.1g) at a dose of 100mg/m2, d1, capecitabine (manufacturer: Shanghai Roche Pharmaceutical Co. H20073024; specification: 0.5g*12 tablets), 1000mg/m2, 2 times/d, d1-14d, orally. One treatment cycle was three weeks and patients were treated for three consecutive cycles.

On the treatment basis of the control group, the experimental group was additionally given an intravenous drip of bevacizumab (manufacturer: Shandong Boan Biotechnology Co., Ltd.; State Drug Quantifier: S20210013; specification: 100mg (4ml)), at a dose of 5mg/kg. The drip duration was maintained at approximately 60-90 min on the first day and was adjusted to 30-45 min thereafter. One treatment cycle was three weeks and patients were treated for three consecutive cycles.

Observation indexes and evaluation criteria

(1) Clinical efficacy was evaluated according to the efficacy evaluation criteria for solid tumors (RECIST version 1.1) (Amano *et al*., 2021), which were classified as complete response (CR): Total disappearance of target lesions, partial response (PR): A reduction of ≥30% in the total length of baseline lesions, stable disease (SD): A reduction in the total length of baseline lesions but not reaching PR or an increase but not reaching PD and progressive disease (PD): an increase of ≥20% in the total length of the baseline lesions or the appearance of new lesions. Response rate (RR) = (PR+CR)/total number of cases × 100%. Disease control rate (DCR) = (CR+PR+SD)/total number of cases × 100%.

(2) 5 ml of fasting venous blood was collected from all patients before and after treatment and centrifuged at 3000 r/min for 20 min to obtain the serum. The serum VEGF level was determined using the ELISA method, and the kit was purchased from Beijing Zhongshan Biotechnology Co. The level of plasma heat shock protein 90α (HSP90α) was determined using the ELSA method, and the kit was purchased from Yantai Progressive Biotechnology Development Co.

(3) Detection of tumor cell apoptosis index: The in situ end-labeling method was used for the assay. Cancerous cells were collected from patients, and the samples were sectioned after incubation with proteinase K, blocked using 3% hydrogen peroxide and finally rinsed with phosphate buffer solution (PBS). Ten fields of view were randomly selected under a 400× microscope (Olympus CX23) and the number of positive cells in 1000 cells was recorded to calculate the apoptosis index. Apoptosis index = positive cells/1000.

(4) The occurrence of adverse reactions during treatment was recorded in the two groups, and the incidence of adverse reactions in the two groups was compared.

(5) The Karnofsky Performance Scale (KPS) was used to assess the quality of patients' survival, with the following evaluation criteria: 100 points: normal no complaints; no evidence of disease. 90 points: able to carry on normal activity; minor signs or symptoms of the disease. 80 points: normal activity with effort; some signs or symptoms of the disease. 70 points: Cares for self; unable to carry on normal activity or to do active work. 60 points: requires occasional assistance, but is able to care for most of the personal needs. 50 points: requires considerable assistance and frequent medical care. 40 points: disabled; requires special care and assistance. 30 points: severely disabled; hospital admission is indicated although death is not imminent. 20 points: very sick; hospital admission necessary; active supportive treatment necessary. 10 points: moribund; fatal processes progressing rapidly. 0 points: dead.

STATISTICAL ANALYSIS

The data processing was performed using SPSS 20.0, and GraphPad Prism 7 (Graph Pad Software, San Diego, USA) was used to visualize the data into graphics. The counting data were expressed as [n (%)] and analyzed using the x2 test and the measurement data were expressed as (x±s) and processed using the t-test. Differences were considered statistically significant when $P<0.05$.

RESULTS

Comparison of clinical data

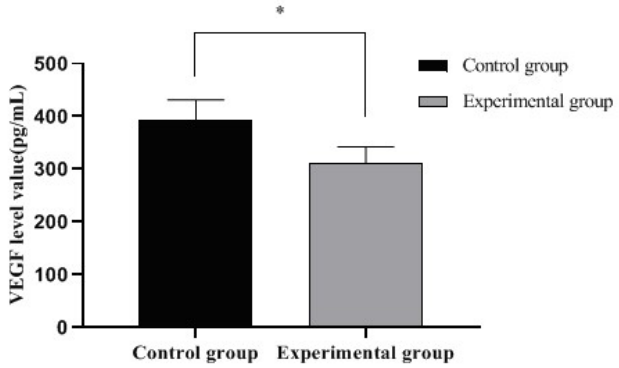
There was no statistical difference ($P>0.05$) in comparison of the clinical data between the two groups, as shown in table 1.

Comparison of clinical efficacy

The effectiveness and disease control rate of the experimental group were 50% and 96%, which were significantly higher than those of 26% and 80% in the control group (P<0.05) (table 2).

Comparison of serum VEGF levels

Markedly lower serum VEGF levels were observed in the experimental group than in the control group after treatment (P<0.05), as shown in fig. 1.



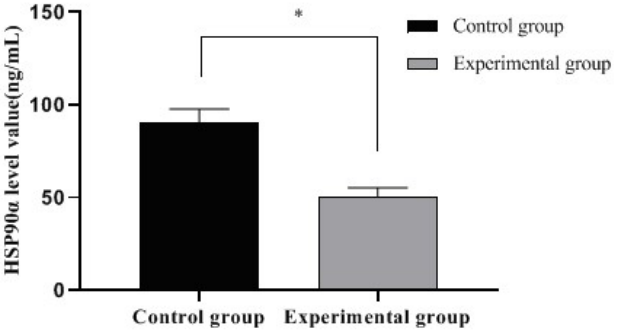
Note: The abscissa indicates the control group and the experimental group; the ordinate indicates the VEGF level, pg/mL.

The VEGF level after treatment in the control group was (394.28±36.77) pg/mL.

The VEGF level in the experimental group after treatment was (312.57±30.06) pg/mL.

* indicates a significant difference in the VEGF levels after treatment between the two groups (t=12.165, p<0.001).

Fig. 1: Comparison of serum VEGF levels after treatment between the two groups (X±S)



Note: The abscissa indicates the control group and the experimental group; the ordinate indicates HSP90α level, ng/mL.

The HSP90α levels after treatment were (90.48±7.23) ng/mL and (50.69±4.67) ng/mL in the control group and the experimental group, respectively.

* indicates a significant difference in HSP90α levels between the two groups after treatment (t=32.689, P<0.001).

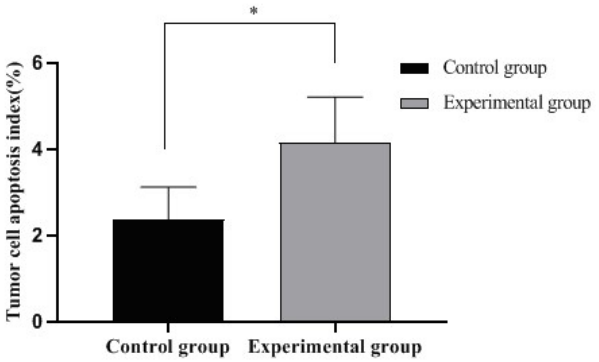
Fig. 2: Comparison of HSP90α levels after treatment between the two groups of patients (X±S)

Comparison of HSP90α levels

The post-treatment HSP90α levels in the experimental group were significantly lower than those in the control group (P<0.05), as detailed in fig. 2.

Comparison of apoptosis index of tumor cells

The experimental group had a significantly higher tumor cell apoptosis index than the control group (P<0.05), as shown in fig. 3.



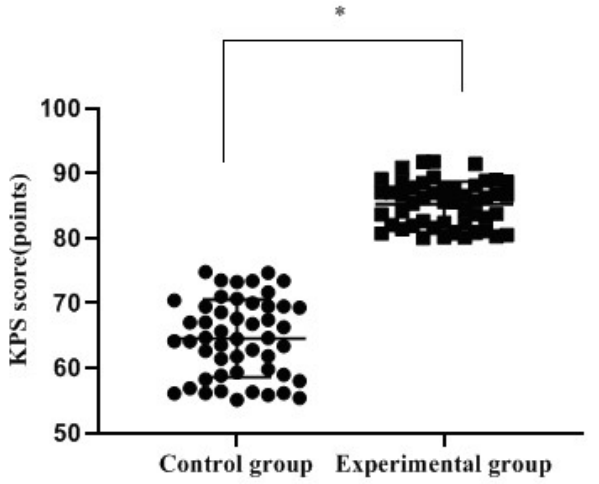
Note: The abscissa indicates the control group and the experimental group; the ordinate indicates the tumor cell apoptosis index, %.

The apoptosis index of tumor cells in the control group after treatment was (2.38±0.74) %.

The apoptosis index of tumor cells in the experimental group after treatment was (4.15±1.06) %.

*indicates a significant difference in the apoptosis index of tumor cells after treatment between the two groups (t=9.682, P<0.001).

Fig. 3: Comparison of apoptosis index of tumor cells after treatment between two groups (X±S)



Note: The abscissa indicates the control group and the experimental group; the ordinate indicates the KPS score, points.

The KPS scores after treatment in the control and experimental groups were (64.57±5.98) and (85.27±3.42), respectively.

*indicates a significant difference in KPS scores between the two groups after treatment (t=21.247, P<0.001).

Fig. 4: Comparison of KPS scores of the two groups (X±S)

Comparison of the incidence of adverse reactions

The incidence of adverse reactions was 8% in the experimental group, which was significantly lower than that of 28% in the control group (P<0.05). See table 3.

Table 1: Comparison of clinical data between the two groups [n (%)]

Items	Control group (n=50)	Experimental group (n=50)	χ^2/t	P
Gender			0.041	0.840
Male	22(44.00)	21(42.00)		
Female	28(56.00)	29(54.00)		
Mean age (year)	57.34±8.92	58.56±9.05	0.679	0.499
Clinical stages				
Pathology stage IV	23(46.00)	20(40.00)	0.367	0.545
Imaging stage IV	27(54.00)	30(60.00)		
Tumor metastasis				
Liver	25(50.00)	26(52.00)	0.040	0.841
Lung	14(28.00)	17(34.00)	0.421	0.517
Lymph node	6(12.00)	4(8.00)	0.444	0.505
Other	5(10.00)	3(6.00)	0.544	0.461
Drinking	18(36.00)	12(38.00)	1.714	0.190
Smoking	19(38.00)	21(42.00)	0.167	0.683
Education level				
University	16(32.00)	15(30.00)	0.047	0.829
Middle school	20(40.00)	22(44.00)	0.164	0.685
Elementary school	14(28.00)	13(26.00)	0.051	0.822

Table 2: Comparison of clinical efficacy between the two groups [n (%)]

Groups	N	CR	PR	SD	PD	RR	DCR
Control group	50	0(0.00)	13(26.00)	27(54.00)	10(12.00)	13(26.00)	40(80.00)
Experimental group	50	0(2.00)	25(50.00)	23(46.00)	2(4.00)	25(50.00)	48(96.00)
X^2						6.112	6.061
P						<0.05	<0.05

Table 3: Comparison of the incidence of adverse reactions in the two groups [n (%)]

Groups	N	Rash	Proteinuria	Hemorrhage	Abnormal bowel movements	Diarrhea	Total incidence
Control group	50	3(6.00)	2(4.00)	2(4.00)	4(8.00)	3(6.00)	14(28.00)
Experimental group	50	1(2.00)	1(2.00)	2(4.00)	0(0.00)	0(0.00)	4(8.00)
X^2							
P							

Comparison of KPS scores

The KPS scores in the experimental group after treatment were significantly higher than those in the control group (P<0.05) (fig. 4).

DISCUSSION

Colorectal cancer is one of the common malignant tumors in China, and its prevalence has shown an increasing trend with social and economic improvement and changes in people's living and eating habits. Clinical symptoms of colorectal cancer, such as blood in stool and abdominal pain, are non-specific, which easily lead to progression of the disease to the middle and advanced stages at the time of diagnosis and loss of optimal treatment timing (Higashijima *et al*., 2021; Wang *et al*., 2021). Chemotherapy is the main treatment for patients with advanced colorectal cancer. Nonetheless, its treatment efficiency in stand-alone treatment has been reported to be under expectation. Recent studies have considered molecular targeted therapy as a new approach for hematological tumors or solid tumors. It mainly targets the characteristics of tumor cells and blocks the invasion of normal cells by tumor cells, thereby inhibiting tumor growth. Therefore, targeted drugs combined with chemotherapy treatment demonstrate great potential as a key approach for the treatment of patients with advanced colorectal cancer (Chen Y. L. *et al*., 2021; Huang L. T. *et al*., 2021; Murakami *et al*., 2021).

VEGF is a highly specific pro-vascular endothelial growth factor that promotes increased vascular permeability, extra cellular matrix degeneration, vascular endothelial cell migration, proliferation, and angiogenesis,

and is, therefore, an important target for tumor therapy (El-Khouly *et al*., 2021; Jorge *et al*., 2021). Bevacizumab is a monoclonal antibody that binds to VEGF to block the binding of VEGF to the surface receptors of vascular endothelial cells, which suppresses endothelial cell proliferation and neovascularization to achieve anti-tumor effects (Tamiya *et al*., 2021). A high expression of VEGF is typical in patients with advanced colorectal cancer. The oxaliplatin-based XELOX chemotherapy regimen is a commonly used treatment regimen applied to patients with advanced colorectal cancer. A study by LI JUN (Li *et al*., 2021) *et al*. showed that bevacizumab combined with chemotherapy for advanced colorectal cancer improved the efficiency of treatment with remarkable effectiveness. Herein, the significantly higher effectiveness and DCR and the lower serum VEGF level in the experimental group compared with the control group indicate the high efficiency of the joint treatment of bevacizumab and chemotherapy in driving down the serum VEGF level in patients with advanced colorectal cancer. Moreover, a marked increase in the apoptosis index of tumor cells in the experimental group than the control group in this study suggests that bevacizumab combined with chemotherapy accelerates tumor cells apoptosis and enhances the prognosis. Prior research has reported a low risk of adverse reactions, mainly including bleeding and proteinuria, in patients after bevacizumab treatment, which had little impact on the subsequent treatment after symptomatic management (Huang C *et al*., 2021). In the present study, the experimental group obtained a remarkably lower incidence of adverse reactions, and no interference with subsequent treatment by adverse events was observed throughout the whole study, indicating a high safety profile of the combination treatment. Furthermore, patients in the experimental group experienced a better post-treatment quality of life than those given chemotherapy only, which confirmed the effectiveness of the combination of bevacizumab and chemotherapy in ameliorating patients' quality of life and controlling disease conditions.

CONCLUSION

In conclusion, bevacizumab combined with chemotherapy for advanced colorectal cancer boosts treatment efficiency, promotes apoptosis of tumor cells, down regulates HSP90α level and enhances patients' quality of life with high safety, which is worthy of clinical promotion and application.

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