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ORIGINAL ARTICLE

Retrospective Cohort Study

Evaluating combined bevacizumab and XELOX in advanced colorectal cancer: Serum markers carcinoembryonic antigen, carbohydrate antigen 125, carbohydrate antigen 199 analysis

Dong-Bing Zhou, Jun Cheng, Xiong-Hui Zhang

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Abstract

BACKGROUND

Colorectal cancer ranks third and second among common and fatal cancers. The treatment of metastatic colorectal cancer (mCRC) is generally based on XELOX in clinical practice, which includes capecitabine (CAP) and oxaliplatin. Serum tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125 and CA199 are prognostic factors for various tumors.

AIM

To investigate evaluating combined bevacizumab (BEV) and XELOX in advanced colorectal cancer: Serum markers CEA, CA125, CA199 analysis.

METHODS

In this retrospective study, a total of 94 elderly patients diagnosed with mCRC were recruited and subsequently categorized into two groups based on the distinct treatment modalities they received. The control group was treated with XELOX plus CAP (n = 47), while the observation group was treated with XELOX plus CAP and BEV (n = 47). Several indexes were assessed in both groups, including disease control rate (DCR), incidence of adverse effects, serum marker levels (CEA, CA125, and CA19) and progression-free survival (PFS).

RESULTS

After 9 wk of treatment, the serum levels of CEA, CA199 and CA125 in the

observation group were significantly lower than those in the control group ($P < 0.05$). Moreover, the PFS of the observation group (9.12 ± 0.90 mo) was significantly longer than that of the control group (6.49 ± 0.64 mo). Meanwhile, there was no statistically significant difference in the incidence of adverse reactions and DCR between the two groups during maintenance therapy ($P > 0.05$).

CONCLUSION

On the basis of XELOX treatment, the combination of BEV and CAP can reduce serum tumor marker levels and prolong PFS in patients with mCRC.

Key Words: Metastatic colorectal cancer; Bevacizumab; Capecitabine; XELOX; Tumor markers

Core Tip: Colorectal cancer has a high incidence in the population. The clinical treatment of colorectal cancer is basically XELOX intervention. Prognostic determination of serum tumor markers is a common index to evaluate the efficacy of cancer drugs. Therefore, we studied the therapeutic effect and serum tumor markers of patients with colorectal cancer under different treatments. The results showed that the therapeutic effect of XELOX + capecitabine (CAP) + bevacizumab was better than that of XELOX + CAP, which showed that the serum carcinoembryonic antigen, carbohydrate antigen (CA) 199 and CA125 levels were lower and the median survival time was longer, and all of them were statistically significant.

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INTRODUCTION

Colorectal cancer (CRC), a common malignant tumor of the digestive tract, ranks third and second among common and fatal cancers, respectively[1,2]. The increase in the incidence rate of CRC is mainly due to the increased exposure to environmental risk factors caused by the westernization of lifestyle and diet[3,4]. About 25 to 30% of CRC cases are associated with unmodifiable risk factors such as genetic factors, personal history of polyps or adenomas, or family history or genetic risk of CRC[5,6]. Approximately 70%-75% of CRC cases are associated with variable risk factors, such as smoking, alcoholism, unhealthy eating, sedentary behavior, lack of physical activity, and obesity[7,8]. Currently, the rising incidence of early-onset CRC poses a serious challenge to global public health[9]. In 2020, the incidence rate of CRC accounted for 10% of global cancers, and according to the prediction of aging, population growth and human development, it is estimated that the number of new CRC cases in the world will reach 3.2 million in 2040[10]. Patients with early CRC usually have a better prognosis through surgery, but about 25% of CRC patients are diagnosed with advanced CRC and have metastasis to distant organs[11].

For patients with advanced metastatic CRC (mCRC) who misses the opportunity for surgery, they can only be treated with high-intensity chemotherapy[12]. The treatment of mCRC is generally based on XELOX in clinical practice, which includes capecitabine (CAP) and oxaliplatin. However, after XELOX treatment, subsequent maintenance therapy usually uses low-intensity and low-toxicity drugs. Capecitabine is a fluorouracil (FU) analogue that can exert cytotoxic effects on tumor cells, but it cannot benefit overall survival (OS) when used alone, so it needs to be used in combination with other drugs. Related studies have shown that adjuvant therapy with targeted drugs can improve efficacy by effectively reducing the damage of chemotherapy to normal cells in the body[13-15]. Bevacizumab (BEV), a monoclonal antibody with targeted effects, can inhibit tumor growth and metastasis by inhibiting the formation of tumor neovascularization caused by the binding of vascular endothelial growth factor (VEGF) to its receptor[16,17]. Research has provided evidence that the utilization of BEV in conjunction with adjuvant chemotherapy can significantly enhance long-term efficacy[18,19]. At present, exploring the efficacy and prognosis of BEV combined with XELOX adjuvant chemotherapy in the treatment of advanced mCRC patients is indispensable.

Some tumor markers also play an important role in the diagnosis, treatment and prognosis assessment of malignant tumors, with the continuous development of molecular biology research. Tumor markers can improve patient adherence and tolerability and are suitable for large-scale screening compared to routine and invasive tests. Carcinoembryonic antigen (CEA), a tumor marker with wide-ranging applicability, is present in various solid malignancies including lung cancer, esophageal cancer, colorectal cancer, and ovarian epithelial cancer. CEA, a broad-spectrum tumor marker, exists in solid malignant tumors, such as lung cancer, esophageal cancer, cancer, colorectal cancer, and ovarian epithelial cancer. Its high preoperative concentration is associated with poor prognosis for CRC patients, and the continuous measurement of CEA can detect recurrent CRC, with a sensitivity of approximately 80% and specificity of approximately 70%[20]. Carbohydrate antigen (CA) 125, also known as mucin 16 or MUC16, is a protein encoded by the MUC16 gene in humans.

According to reports, CA125 is a significant and independent prognostic factor for colorectal cancer patients who outperform CEA[21]. Regardless of peritoneal metastasis, CRC patients with elevated preoperative CA125 Levels have lower OS and CSS rates[22]. CA199 is a diagnostic indicator for various malignant tumors, which belongs to the category of macromolecular glycoproteins and contains mucus[23]. CA199 has been reported as a valuable indicator for predicting the risk of CRC[24]. Therefore, the combined detection of CEA, CA125, and CA199 is of great significance in evaluating the prognosis of mCRC.

This study mainly explores the efficacy and prognosis of BEV combined with XELOX adjuvant chemotherapy in patients with advanced mCRC by detection of serum levels of CEA, CA199 and CA125.

MATERIALS AND METHODS

General information

This study encompassed a retrospective analysis of 94 elderly patients diagnosed with advanced mCRC who received treatment at the hospital between November 2020 and November 2022. The baseline characteristics of mCRC patients are given in Table 1. This study was reviewed and approved by the medical ethics committee of the hospital and executed in accordance with the Helsinki Declaration.

Inclusion and exclusion criteria

The inclusion criteria were as follows: metastatic lesions in mCRC patients mCRC could not be surgically removed and distant metastasis was limited to a single organ or site; the Eastern Cooperative Oncology Group (ECOG) score of mCRC patients was 0-2 points; bone marrow function met the standard; the survival in patients with mCRC was estimated to be greater than 3 mo and patients with mCRC had stable disease (SD) or above after chemotherapy with 4 XELOX regimens. Exclusion criteria were as follows: patients with mCRC had active infection, other malignancies, severe endocrine disease, intestinal obstruction or large ascites.

Treatment methods

All patients were divided into the observation group (n = 47) and the control group (n = 47) according to the different treatment methods. Both groups were treated with XELOX as follows: Oxaliplatin was administered intravenously for 2 h on the first day of the cycle (130 mg/m^2) and CAP tablets were orally administered twice a day for 14 d (1000 mg/m^2), with discontinuation for 7 d. One chemotherapy cycle was 21 d, and the patient was treated for 4 cycles. After achieving SD or better status through first-line chemotherapy, the control group received maintenance treatment with CAP twice a day for 14 d orally (1000 mg/m^2), followed by discontinuation for 7 d, with 21 d as a cycle. The difference was that the observation group was combined with BEV on the basis of the control group. Specifically, BEV was given for 60-90 min intravenously (7.50 mg/kg) on the first day of the cycle, with 21 d as a cycle. Both groups were subjected to maintenance treatment until disease progression or intolerable adverse reactions occurred.

Outcome indicators

After the end of chemotherapy, efficacy evaluation was carried out based on the evaluation criteria for solid tumor efficacy. Complete remission (CR) referred to the disappearance of all lesions; Partial remission (PR) was a reduction in lesion radius by more than 30%; SD referred to a decrease in lesion radius of less than or equal to 30% or an increase of less than 20%; The progression of disease (PD) was an increase in lesion radius of ≥ 20%. The equation for disease control rate (DCR) was the sum of CR, PR and SD cases/total cases × 100%. Follow up was performed by phone every 2 wk after chemotherapy and PFS was recorded. In addition, the patient's serum levels of CEA, CA125, and CA199 were detected before and after chemotherapy.

Statistical analysis

The data analysis was conducted using SPSS 22.0 software. The measurement data expressed as mean ± SD and compared by using Student's t-tests. The counting data expressed as n (%) and compared by using χ^2 test. $P < 0.05$ had a statistical significance.

RESULTS

Comparison of baseline characteristics

A total of 94 patients, who satisfied the predetermined inclusion and exclusion criteria, were incorporated into the present study. As shown in Table 1, The average age of mCRC patients in the observation and control groups was 72.25 ± 6.41 (range 60-82 years) and 72.19 ± 6.37 (range 60-83 years). The male to female distribution ratios of patients with mCRC in the observation group and control group were 23:24 and 22:25, respectively. The primary lesion of both groups of mCRC patients was located in the left-sided colorectal or right-sided colon, with liver, bone, lung, or abdominal metastasis. There was no significant difference in baseline characteristics between the two groups.

Table 1 Baseline characteristics of patients in the two groups

Group	Gender (male/female)	Age (yr)	Average age (yr)	Primary lesion site (*n*)		Metastasis site (*n*)			
				Left-sided colorectal	Right-sided colon	Liver	Bone	Lung	Abdominal cavity
Observation group (*n* = 47)	23/24	60-83	72.25 ± 6.41	31	16	19	12	11	5
Control group (*n* = 47)	22/25	60-82	72.19 ± 6.37	30	17	18	13	10	6

Table 2 Recent therapeutic effects in the two groups

Group	CR	PR	SD	PD	DCR
Observation group (*n* = 47)	0	11 (23.40)	17 (36.17)	19 (40.43)	28 (59.57)
Control group (*n* = 47)	0	10 (21.28)	16 (34.04)	21 (44.68)	26 (55.32)
χ^2					0.174
P value					0.677

CR: Complete remission; PR: Complete remission; SD: Stable disease; PD: Progression of disease; DCR: Disease control rate.

Table 3 Incidence of adverse reactions during treatment in the two groups

Group	HFSR	Anemia	Hepatic insufficiency	Weakness	Nausea and vomiting	Neutropenia
Observation group (*n* = 47)	10 (21.28)	2 (4.26)	2 (4.26)	7 (14.89)	14 (29.79)	14 (29.79)
Control group (*n* = 47)	9 (19.15)	1 (2.13)	2 (4.26)	5 (10.64)	12 (25.53)	12 (25.53)
χ^2	0.066	0	0.261	0.382	0.213	0.213
P value	0.797	1	0.609	0.536	0.645	0.645

HFSR: Hand-foot skin reaction.

Changes in CR, PR, SD, PD and DCR indicators after treatment

After 9 wk of maintenance treatment, there were no cases of CR in both groups. Among them, the PR, SD, and DCR of the observation group were higher than those of the control group, while the PD was lower than those of the control group. Unfortunately, these values were not statistically significant between the two groups ($P > 0.05$) (Table 2).

Changes in the incidence of adverse reactions between the two groups

There was no significant difference in the severity of hand-foot skin reaction, anemia, hepatic insufficiency, weakness, nausea and vomiting and neutropenia between the observation and control groups during chemotherapy ($P > 0.05$) (Table 3).

Changes in CEA, CA125 and CA19 indicators and PFS after treatment

There was no significant difference in serum levels of CEA, CA199 and CA125 between the two groups before maintenance therapy ($P > 0.05$). After 9 wk of maintenance treatment, the serum levels of CEA, CA199 and CA125 between the two groups were lower than before treatment, and the serum levels of CEA, CA199 and CA125 levels in the observation group were lower than those in the control group after treatment ($P < 0.05$) (Table 4 and Figure 1). Furthermore, the PFS of the observation group was 9.12 ± 0.90 mo, which was longer than the 6.49 ± 0.64 mo of the control group ($P < 0.05$) (Figure 2).

DISCUSSION

There are many factors that contribute to the occurrence of CRC in the body, such as diet, lifestyle habits, environment, and genetics[25]. So far, radical surgery is the only method to cure CRC. However, patients generally develop into distant metastases and are in the advanced stage at the time of diagnosis, which leads to the loss of surgical opportunities for patients[26,27]. Currently, mCRC can be treated with the XELOX regimen, which can inhibit cancer cell proliferation and

Table 4 Levels of serum carcinoembryonic antigen, carbohydrate antigen 199, carbohydrate antigen 125 in the two groups

Group	CEA (μg/mL)		CA199 (U/mL)		CA125 (U/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n = 47)	8.22 ± 0.76	1.53 ± 0.12[a]	50.63 ± 4.75	20.67 ± 2.01[a]	72.90 ± 7.04	43.09 ± 5.63[a]
Control group (n = 47)	8.35 ± 0.71	3.91 ± 0.19[a]	51.22 ± 4.92	39.54 ± 2.76[a]	72.83 ± 7.12	45.13 ± 6.97[a]
χ^2	0.857	72.607	0.591	37.889	0.038	2.247
P value	0.3197	< 0.001	0.278	< 0.001	0.97	0.0217

[a]P < 0.05. Serum tumor marker levels of carcinoembryonic antigen, carbohydrate antigen (CA) 199 and CA125 in the control and observation groups. CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen.

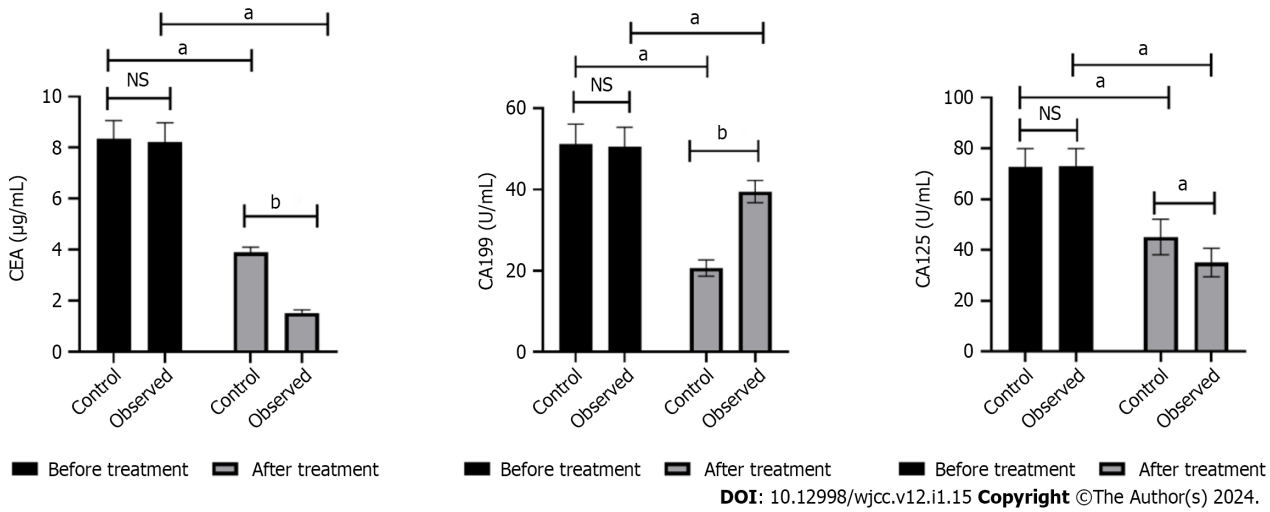

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Figure 1 Serum tumor marker levels of carcinoembryonic antigen, carbohydrate antigen 199 and carbohydrate antigen 125 in the control and observation groups. [a]P < 0.05 and [b]P < 0.001.

prolong patient survival time[28,29]. However, oxaliplatin in the XELOX regimen has certain toxicity and cannot be used for a long time, so the significance of taking low-intensity and low-toxicity drugs for treatment is even greater[30].

CAP is a new generation of FU drugs, which can effectively kill tumor cells due to thymidine phosphorylase transformation in the body[31]. At the same time, it has obvious therapeutic effect on malignant tumors, but has no effect on normal tissues basically, which is because thymidine phosphorylase exists in tumor tissues generally[32-34]. BEV is a molecularly targeted drug, which can competitively bind to vascular endothelial growth factor receptors in the body, resulting in slow generation of new blood vessels, and finally allowing the disease to be controlled to a certain extent[35-37]. In this study, there was no statistically significant difference in the incidence of adverse reactions and DCR between the two groups during maintenance treatment for 9 wk, indicating that the two regimens had the same short-term efficacy and safety.

So far, tumor marker indicators can reflect tumor burden to a certain extent, including CEA, CA199, and CA125[38-40]. After 9 wk of maintenance therapy, serum levels of CEA, CA199 and CA125 in the observation group were lower than those in the control group and PFS was longer than in the control group. After XELOX treatment, the tumor cells in the patient's body were effectively killed and the small metastatic lesions in the body were also cleared. When the disease reaches a stable state, bevacizumab combined with capecitabine acts on tumor cells and vascular endothelial cells to produce sustained anti-tumor effects, which can not only consolidate the efficacy of first-line chemotherapy but also reduce the cumulative toxicity of drugs, delay tumor progression and reduce tumor burden, and ultimately leading to a prolonged survival time for patients. However, there are some limitations in this study. The sample size is a bit small. Further studies were needed to overcome these limitations to make the data more convincing.

CONCLUSION

In summary, on the basis of XELOX treatment, the maintenance treatment of BEV combined with CAP can reduce serum tumor marker levels of CEA, CA199, and CA125 and prolong PFS.

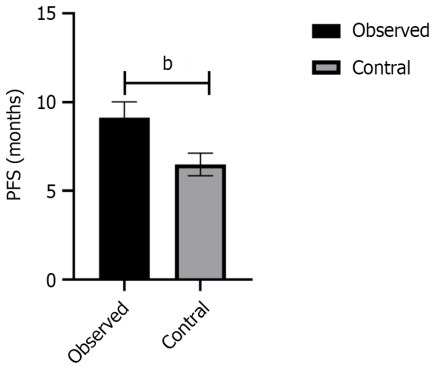

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Figure 2 Progression-free survival of metastatic colorectal cancer patients in the control and observation groups. $^{b}P < 0.001$. PFS: Progression-free survival.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer is ranked as the third most common and second most fatal cancer. In clinical practice, the treatment of metastatic colorectal cancer (mCRC) typically relies on the administration of XELOX, a combination therapy involving capecitabine (CAP) and oxaliplatin. Additionally, serum tumor markers such as carcinoembryonic antigen, carbohydrate antigen (CA) 125, and CA199 serve as prognostic indicators for a range of tumors.

Research motivation

The impact of the combination of bevacizumab (BEV) and XELOX chemotherapy on individuals diagnosed with advanced mCRC.

Research objectives

The objective of this study is to examine the impact of the combination of BEV and XELOX chemotherapy on individuals diagnosed with advanced mCRC, as well as the alterations observed in their serum tumor markers.

Research methods

A comprehensive analysis was conducted on the 94 cases within our hospital, wherein the data was meticulously compared across various treatment modalities.

Research results

Multiple indexes were evaluated in both groups.

Research conclusions

Based on the utilization of XELOX treatment, the incorporation of BEV and CAP has demonstrated the ability to diminish serum tumor marker levels and extend progression-free survival among patients diagnosed with mCRC.

Research perspectives

The addition of Bevacizumab to first-line chemotherapy demonstrated a greater benefit in comparison to chemotherapy alone.

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FOOTNOTES

Co-first authors: Dong-Bing Zhou and Jun Cheng.

Author contributions: Zhou DB and Cheng J designed the research; Zhang XH, Zhou DB, and Cheng J performed the research; Zhang XH, Zhou DB, and Cheng J contributed new reagents/analytic tools; Zhang XH, Zhou DB, and Cheng J analyzed the data; Zhou DB and Cheng J wrote the paper; All authors were involved in the critical review of the results and have contributed to, read, and approved the

final manuscript. Zhou DB and Cheng J contributed equally to this work as co-first authors equally to this work. The reasons for designating Zhou DB and Cheng J as co-first authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Zhou DB and Cheng J contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Zhou DB and Cheng J as co-first authors of is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

Institutional review board statement: This study protocol was approved by Xiantao First People's Hosepital Affiliated to Yangtze University, and all the families have voluntarily participated in the study and have signed informed consent forms.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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