World Journal of

Gastrointestinal Surgery

World Journal of Gastrointestinal Surgery

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Monthly Volume 15 Number 5 May 27, 2023

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Surgery* (*WJGS*, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

   WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc*.

INDEXING/ABSTRACTING

The *WJGS* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJGS* as 2.505; IF without journal self cites: 2.473; 5-year IF: 3.099; Journal Citation Indicator: 0.49; Ranking: 104 among 211 journals in surgery; Quartile category: Q2; Ranking: 81 among 93 journals in gastroenterology and hepatology; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

ORIGINAL ARTICLE

Retrospective Study

Retrospective efficacy analysis of olaparib combined with bevacizumab in the treatment of advanced colorectal cancer

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Abstract

BACKGROUND

Colorectal cancer (CRC) is a highly prevalent malignancy of the digestive tract worldwide, characterized by a significant morbidity and mortality rate and subtle initial symptoms. Diarrhea, local abdominal pain, and hematochezia occur with the development of cancer, while systemic symptoms such as anemia and weight loss occur in patients with advanced CRC. Without timely interventions, the disease can have fatal consequences within a short span. The current therapeutic options for colon cancer include olaparib and bevacizumab, which are widely utilized. This study intends to evaluate the clinical efficacy of olaparib combined with bevacizumab in the treatment of advanced CRC, hoping to provide insights into advanced CRC treatment.

AIM

To investigate the retrospective efficacy of olaparib combined with bevacizumab in the treatment of advanced CRC.

METHODS

A retrospective analysis was conducted on a cohort of 82 patients with advanced colon cancer who were admitted to the First Affiliated Hospital of the University of South China between January 2018 and October 2019. Among them, 43 patients subjected to the classical FOLFOX chemotherapy regimen were selected as the control group, and 39 patients undergoing treatment with olaparib combined with bevacizumab were selected as the observation group. Subsequent to different treatment regimens, the short-term efficacy, time to progression (TTP), and incidence rate of adverse reactions between the two groups were compared. Changes in serum-related indicators [vascular endothelial growth factor (VEGF),

matrix metalloprotein-9 (MMP-9), cyclooxygenase-2 (COX-2)] and tumor markers [human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199)] levels before and after treatment were compared between the two groups at the same time.

RESULTS
The objective response rate was discovered to be 82.05%, and the disease control rate was 97.44% in the observation group, which were significantly higher than the respective rates of 58.14% and 83.72% in the control group ($P < 0.05$). The median TTP was 24 mo (95%CI: 19.987-28.005) in the control group and 37 mo (95%CI: 30.854-43.870) in the observation group. The TTP in the observation group was significantly better than that in the control group, and the difference held statistical significance (log-rank test value = 5.009, $P = 0.025$). Before treatment, no substantial difference was detected in serum VEGF, MMP-9, and COX-2 levels and tumor markers HE4, CA125, and CA199 levels between the two groups ($P > 0.05$). Following treatment with different regimens, the above indicators in the two groups were remarkably promoted ($P < 0.05$), VEGF, MMP-9, and COX-2 in the observation group were lower than those in the control group ($P < 0.05$), and HE4, CA125, and CA199 levels were also lower than those in the control group ($P < 0.05$). Vis-à-vis the control group, the total incidence of gastrointestinal reactions, thrombosis, bone marrow suppression, liver and kidney function injury, and other adverse reactions in the observation group was notably lowered, with the difference considered statistically significant ($P < 0.05$).

CONCLUSION
Olaparib combined with bevacizumab in the treatment of advanced CRC demonstrates a strong clinical effect of delaying disease progression and reducing the serum levels of VEGF, MMP-9, COX-2 and tumor markers HE4, CA125 and CA199. Moreover, given its fewer adverse reactions, it can be regarded as a safe and reliable treatment option.

Key Words: Olaparib; Bevacizumab; Advanced colorectal cancer; Efficacy

Core Tip: Colorectal cancer (CRC) presents insignificant symptoms in the early stage and is commonly diagnosed in the middle and advanced stages. Therefore, surgery is usually not viable because the best timing is missed, and chemotherapy, targeted therapies and other regimens are often utilized as interventions. Olaparib and bevacizumab are common targeted therapies with excellent therapeutic effects in a variety of solid tumors. This research collected the clinical data of 82 patients with advanced CRC, retrospectively investigated the clinical efficacy and safety of olaparib combined with bevacizumab in advanced CRC treatment, and analyzed the effect of this treatment regimen on the serum levels of vascular endothelial growth factor, matrix metalloprotein-9, cyclooxygenase-2, and related tumor markers.

INTRODUCTION

Colorectal cancer (CRC), a malignant tumor disease of the digestive tract originating from the epithelial tissues of the colon or rectal mucosa, is the third most prevalent cancer worldwide and the fourth leading contributor to cancer-related death[1-3]. Epidemiological statistics show that as of 2018, approximately 1.8 million new CRC pathologies were reported worldwide, resulting in 881000 deaths, underscoring the considerable harmful consequences of this disease[4]. Over the past five decades, the incidence and mortality of colon cancer have increased year by year in young and middle-aged people (< 50 years old), with an annual increase of 2% in individuals < 50 years old since 1994, leading to a surge in CRC incidence in younger age groups[5]. According to different histological types, colon cancer can be classified into three categories: adenocarcinoma, mucinous adenocarcinoma, and undifferentiated carcinoma[6,7]. Early-stage colon cancer often lacks obvious clinical symptoms and is easily neglected. Progressing to the middle and later stages, the disease often demonstrates abdominal pain, abdominal distension, diarrhea, hematochezia, and other symptoms. Moreover, about 20%-50% of patients have developed distant organ metastasis to varying degrees at the time of diagnosis[8], which

seriously impacts patient survival and prognosis.

At present, colon cancer is predominantly treated with surgical resection, but this approach is not suitable for advanced metastatic colon cancer. Chemotherapeutic drugs such as 5-fluorouracil, oxaliplatin, and olaparib are used clinically for first-line targeted chemotherapy[9,10]. In addition, with the continuous improvement of targeted molecular therapies, treatment strategies targeting vascular endothelial growth factor (VEGF) as well as epidermal growth factor (EGF) receptors have been demonstrated to heighten the survival rate of patients with advanced colon cancer[11,12]. Bevacizumab, an anti-angiogenic targeted therapeutic agent with strong anti-tumor activities, has been applied in the clinical treatment of malignant solid tumors such as breast cancer, non-small cell lung cancer, and CRC, and has achieved certain results[13,14]. Nevertheless, the efficacy of olaparib combined with bevacizumab in the clinical treatment of patients with advanced colon cancer remains less well studied. Based on this, 82 cases of advanced CRC patients admitted to the First Affiliated Hospital of the University of South China were collected for retrospective analysis in this study so as to investigate the efficacy of olaparib combined with bevacizumab in advanced CRC treatment. It's expected to offer more effective data support for the clinical application of this treatment regimen in advanced CRC.

MATERIALS AND METHODS

General information
Eighty-two patients with advanced colon cancer admitted to the First Affiliated Hospital of the University of South China from January 2018 to October 2019 were enrolled as the subjects of this retrospective study. The control group consisted of 43 patients who received the classical FOLFOX chemotherapy regimen, while the observation group included 39 patients who received olaparib combined with bevacizumab. The control group was composed of 24 males and 19 females, with age ranging from 22 to 71 years (average age: 46.02 ± 7.28 years), while the observation group encompassed 19 males and 20 females aged between 21-73 years (mean age: 48.37 ± 6.41 years). There was no remarkable statistical difference in gender, age, body mass index, histological type, and tumor-node-metastasis stage between the two groups ($P > 0.05$), as shown in Table 1, indicating the comparability of the two groups.

Inclusion and exclusion criteria
Inclusion criteria: Participants were aged 18 years or older; diagnosed with advanced colon cancer by magnetic resonance imaging, computed tomography, and other imaging examinations combined with pathological section, cytological examination, and clinical diagnosis; and were at stage III-IV according to the eighth edition of the American Joint Committee on Cancer Staging Manual[15]. Additionally, patients were required to have at least one objective measurable tumor lesion, blood routine, electrocardiogram, and other biochemical tests before treatment. Participants with no history of drug allergy and complete clinical data were included in the study.

Exclusion criteria: Patients with liver cancer, gastric cancer, and other malignant tumor diseases; patients with blood diseases or autoimmune diseases; patients with heart, liver and kidney, and other vital organ dysfunction; patients who received radiotherapy or other regimens of chemotherapy before enrollment; patients with hypertension, diabetes, heart disease, and other underlying diseases; patients with mental disorders, Alzheimer's disease or other cognitive impairment; patients during pregnancy and lactation; an expected survival of fewer than 3 mo.

Treatment regimen
The control group (43 patients) received classical FOLFOX chemotherapy, which consisted of oxaliplatin (Zhejiang Hisun Pharmaceutical Co., Ltd.; approval number: GYZZ H20093487) administered intravenously at a dose of 135 mg/m² for 2 h on day 1, calcium folinate (Jiangsu Hengrui Medicine Co., Ltd.; approval number: GYZZ H20000418) administered at 200 mg/m² for 2 h on days 1-3, and 5-fluorouracil (Hainan Zhuotai Pharmaceutical Co., Ltd.; approval number: GYZZ H20051626) given continuously by an intravenous pump at a dose of 2600 mg/m² for 46-48 h, every 3 weeks for a total of 6 cycles of chemotherapy.

The observation group (39 patients) underwent the treatment of olaparib combined with bevacizumab. To wit, olaparib (AstraZeneca; registration certificate number: H20180049) was taken orally at a dose of 200 mg twice daily- once in the morning and once in the evening; bevacizumab injection (Shanghai Roche Pharmaceutical Co., Ltd.; approval No.: S20120068) was intravenously injected at 15 mg/kg for 0.5-1 h on day 1, every three weeks for a total of six cycles of chemotherapy.

Clinical assay items
Short-term efficacy: As per the iRECIST response evaluation criteria for cancer immunotherapy [16], the efficacy of both patient groups was assessed at the conclusion of treatment. Short-term efficacy was categorized into immune complete response (iCR), immune partial response (iPR), immune stable

Table 1 Comparison of general data between the two groups

General information	Control group (*n* = 43)	Observation group (*n* = 39)	*t*/χ^2	*P* value
Gender (*n*)			0.413	0.521
Male	24	19		
Female	19	20		
Age (yr), mean ± SD	46.02 ± 7.28	48.37 ± 6.41	1.545	0.126
BMI (kg/m^2), mean ± SD	22.45 ± 3.46	23.01 ± 2.98	0.781	0.437
Histological classification (*n*)			0.427	0.808
Adenocarcinoma	27	22		
Mucinous cancer	12	12		
Undifferentiated carcinoma	4	5		
TNM stage (*n*)			2.201	0.138
III	12	17		
IV	31	22		

BMI: Body mass index; TNM: Tumor-node-metastasis.

disease (iSD) and immune progressive disease (iPD). Among them, iCR was identified as tumor changes disappeared and clinical symptoms improved; iPR was recognized upon lessened tumor volume and no detection of new tumor metastasis or lesion; iSD was identified when the tumor volume was reduced (degree of reduction less than 25%), and no new metastasis or lesion occurred; iPD was recognized when the tumor volume barely changed, and the number of distant metastasis and lesion increased instead. Objective response rate (ORR) = (iCR + iPR)/total number of patients > 100%, disease control rate (DCR) = (iCR + iPR + iSD)/total number of patients > 100%.

Time to progression (TTP): The time required from grouping to objective tumor progression was observed and counted for both groups during the follow-up period. Non-progression and survivors were considered censored data following the conclusion of the follow-up.

Serum-related parameters: Before treatment and after six treatment cycles, 5 mL fasting venous blood was harvested from each patient in both groups. The serum was separated after high-speed centrifugation and stored in an ultra-low temperature freezer at -80 °C for later use. Serum levels of VEGF, MMP-9, and COX-2 were determined using an enzyme-linked immunosorbent assay[17]. VEGF kits were purchased from Beijing Zhongshan Biotechnology Co., Ltd., MMP-9 kits were bought from Anhui Anke Biological Co., Ltd., and COX-2 kits were purchased from Shanghai Kaibo Biochemical Reagent Co., Ltd. All procedures were performed in strict accordance with the kit instructions.

Tumor markers: Prior to treatment and subsequent to six treatment cycles, 5 mL fasting venous blood was collected from each patient in the two groups. The serum was separated after high-speed centrifugation and stored in an ultra-low temperature freezer at -80 °C for later use. The levels of tumor markers HE4, CA125, and CA199 in serum samples were confirmed through enzyme-linked immunosorbent assay [18] with the assistance of an ST-360 automatic enzyme-linked immunosorbent assay analyzer (Shanghai Kehua Experimental Instrument Co., Ltd.). The kits were purchased from Shanghai Youkewei Biotechnology Co., Ltd. All operations were conducted in strict accordance with the kit instructions.

Adverse reactions: Gastrointestinal reactions, thrombosis, bone marrow suppression, and liver and kidney function injury, and other adverse reactions and symptoms were closely observed, recorded, and analyzed in both groups, and the incidence was calculated.

Statistical analysis

All data in this study were processed and analyzed using SPSS 22.0 software. Measurement data were presented as mean ± SD, and *t*-test was applied for analysis. Enumeration data were represented as percentages, and χ^2 test was used for analysis. The Kaplan-Meier method was utilized to calculate the TTP. When *P* < 0.05, statistical significance was determined.

RESULTS

Comparison of short-term efficacy between the two groups

Following distinct treatment strategies, a comparative evaluation of short-term efficacy was conducted between the two groups. The results showed that ORR attained 82.05%, while DCR was 97.44% in the observation group, which were higher than the respective rates of 58.14% and 83.72% in the control group. As highlighted in Table 2, there was a notable difference in the short-term efficacy between the two groups ($P < 0.05$).

Comparison of time to disease progression between the two groups

The Kaplan-Meier analysis displayed that the median TTP was 24 mo (95%CI: 19.987-28.005) in the control group and 37 mo (95%CI: 30.854-43.870) in the observation group, which was better than that in the control group (Figure 1). The difference was statistically meaningful (log-rank test value = 5.009, $P = 0.025$).

Comparison of serum-related index levels between the two groups

Prior to treatment, no substantial difference was observed in serum VEGF, MMP-9, and COX-2 levels between the two groups ($P > 0.05$). After the adoption of different treatment methods, the above indicators were improved in both groups ($P < 0.05$). VEGF, MMP-9, and COX-2 in the observation group were 294.81 ± 20.63 pg/mL, 200.43 ± 15.02 mg/L, and 311.36 ± 22.14 ng/L, respectively. In contrast, the control group exhibited higher levels of these indicators (375.60 ± 22.05 pg/mL, 256.78 ± 17.62 mg/L, and 523.41 ± 27.48 ng/L, respectively), as presented in Table 3. The difference held statistical significance ($P < 0.05$).

Comparison of tumor marker levels between the two groups

Prior to treatment, there was no discernible difference in the levels of tumor markers HE4, CA125, and CA199 between the two groups ($P > 0.05$). After distinct treatment strategies, the above indicators in the two groups were vigorously bolstered ($P < 0.05$). HE4, CA125 and CA199 in the observation group were 121.36 ± 19.48 pmol/L, 35.61 ± 4.25 ng/mL and 56.37 ± 7.41 U/mL, respectively. On the contrary, the control group had higher levels of the above indicators (184.65 ± 22.34 pmol/L, 58.56 ± 6.08 ng/mL, and 82.84 ± 9.28 U/mL, respectively), as displayed in Table 4. The difference held statistical significance ($P < 0.05$).

Comparison of the incidence of adverse reactions between the two groups

The total incidence rate of adverse reactions, including gastrointestinal reactions, thrombosis, bone marrow suppression, and liver and kidney function injury, was significantly lower in the observation group (5.12%) compared to the control group (20.94%), as indicated in Table 5. The difference was statistically significant ($P < 0.05$). Timely symptomatic treatment ameliorated the adverse reactions for patients in both groups and had no substantial impact on the implementation of this treatment plan.

DISCUSSION

According to global cancer incidence and mortality statistics, colon cancer has emerged as the second most common cancer worldwide, surpassed only by lung cancer, with an incidence rate as high as 10.2% and a mortality rate of 9.2%[19]. CRC exhibits no evident specific symptoms in the early stage and is mostly screened out during routine health examinations. However, patients are typically diagnosed when they seek medical treatment for hematochezia, diarrhea, abdominal pain, weight loss, anemia, and weight loss, at which point they are usually in the middle or advanced stage. Tumor lesions and metastases can severely impair the patient's physical condition, and invasive surgical resection or treatment methods with greater toxicity and side effects may not be suitable for advanced patients[20, 21]. Therefore, it is of paramount significance to explore effective treatment plans for advanced CRC that prolong the patient's life cycle and improve their quality of life.

The primary treatment for early-stage colon cancer is surgical resection of the tumor lesion. However, for advanced colon cancer, the high degree of malignancy and strong metastasis pose significant clinical challenges[22,23]. In a survey of 7786 patients who underwent resection of colon cancer, Moghadamyeghaneh *et al*[24] reported that approximately 10.8% of patients developed metastases at the time of surgery, and patients with metastatic colon cancer displayed higher postoperative morbidity and mortality than those with localized colon cancer. At present, for the treatment of advanced colon cancer, cytotoxic drugs such as 5-fluorouracil, oxaliplatin, capecitabine, and irinotecan combined with biological agents such as cetuximab, panitumumab, and bevacizumab are mainly used for chemotherapy, with good clinical efficacy in improving progression-free survival and overall survival rates[25-27]. Based on previous studies, this study compared the short-term efficacy, time to progression, incidence of adverse reactions, and changes in serum VEGF, MMP-9, COX-2 levels and

Table 2 Comparison of short-term efficacy between the two groups, *n* (%)

Group	iCR	iPR	iSD	iPD	ORR	DCR
Control group (*n* = 43)	9 (20.93)	16 (37.21)	11 (25.58)	7 (16.28)	25 (58.14)	36 (83.72)
Observation group (*n* = 39)	20 (51.28)	12 (30.77)	6 (15.38)	1 (2.56)	32 (82.05)	38 (97.44)
χ^2					5.518	4.369
P value					0.019	0.037

ORR: Objective response rate; DCR: Disease control rate; iCR: Immune complete response; iPR: Immune partial response; iSD: Immune stable disease; iPD: Immune progressive disease.

Table 3 Comparison of serum-related index levels between the two groups

Group	VEGF (pg/mL)		MMP-9 (mg/L)		COX-2 (ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (*n* = 43), mean ± SD	421.38 ± 36.41	375.60 ± 22.05[a]	301.25 ± 26.73	256.78 ± 17.62[a]	711.39 ± 54.43	523.41 ± 27.48[a]
Observation group (*n* = 39), mean ± SD	427.91 ± 37.23	294.81 ± 20.63[a]	308.43 ± 22.08	200.43 ± 15.02[a]	718.43 ± 49.26	311.36 ± 22.14[a]
t	0.802	17.083	1.318	15.504	0.612	38.227
P value	0.425	< 0.001	0.191	< 0.001	0.542	< 0.001

[a]$P < 0.05$ *vs* before treatment in the same group. VEGF: Vascular endothelial growth factor; MMP-9: Matrix metalloprotein-9; COX-2: Cyclooxygenase-2.

Table 4 Comparison of tumor marker levels between the two groups

Group	HE4 (pmol/L)		CA125 (ng/mL)		CA199 (U/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (*n* = 43), mean ± SD	343.75 ± 51.26	184.65 ± 22.34[a]	82.43 ± 11.27	58.56 ± 6.08[a]	119.60 ± 15.62	82.84 ± 9.28[a]
Observation group (*n* = 39), mean ± SD	349.81 ± 45.79	121.36 ± 19.48[a]	83.26 ± 10.33	35.61 ± 4.25[a]	121.03 ± 19.85	56.37 ± 7.41[a]
t	0.562	13.610	0.346	19.618	0.364	14.177
P value	0.576	< 0.001	0.730	< 0.001	0.717	< 0.001

[a]$P < 0.05$ *vs* before treatment in the same group. HE4: Human epididymis protein 4; CA125: Carbohydrate antigen 125; CA199: Carbohydrate antigen 199.

Table 5 Comparison of incidence rate of adverse reactions between the two groups, *n* (%)

Group	Gastrointestinal reactions	Thrombus	Myelosuppression	Hepatic and renal impairment	Total incidence
Control group (*n* = 43)	4 (9.30)	1 (2.33)	3 (6.98)	1 (2.33)	9 (20.94)
Observation group (*n* = 39)	1 (2.56)	0 (0)	0 (0)	1 (2.56)	2 (5.12)
χ^2					4.397
P value					0.036

tumor markers HE4, CA125, and CA199 levels before and after treatment in advanced colon cancer patients treated with the standard FOLFOX chemotherapy of 5-fluorouracil, oxaliplatin, and Calcium Folinate combination, as well as the chemotherapy using olaparib combined with bevacizumab.

In this study, 43 patients in the control group treated with standard FOLFOX chemotherapy and 39 patients in the observation group treated with olaparib combined with bevacizumab chemotherapy

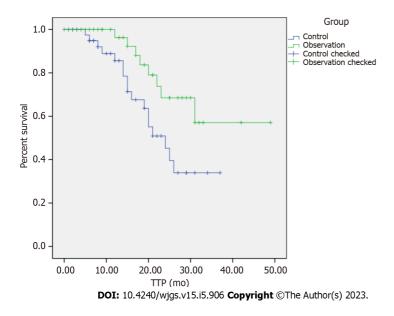**DOI:** 10.4240/wjgs.v15.i5.906 **Copyright** ©The Author(s) 2023.

Figure 1 Comparison of time to disease progression between control group and observation group. TTP: Time to progression.

were retrospectively analyzed to compare the clinical efficacy, disease progression time and adverse reactions between the two strategies during advanced CRC treatment. The outcomes demonstrated that ORR and DCR in the observation group were higher than those in the control group, the disease progression time was longer than that in the control group, while the total incidence of adverse reactions was lower than that in the control group, indicating that olaparib combined with bevacizumab in the treatment of advanced CRC not only had excellent short-term efficacy, but also prolonged the disease progression of patients, and had smaller toxic and side effects. As compared with the classical FOLFOX chemotherapy, it was safer and more reliable, with better clinical efficacy. FOLFOX chemotherapy is a widely used approach for the clinical management of CRC. Nonetheless, its clinical application may result in bone marrow suppression, digestive system disorders, and nervous system reactions, resulting in significant adverse effects on the patients [28]. Furthermore, studies have reported that approximately 60% of patients with CRC do not respond adequately to FOLFOX chemotherapy [29]. Kim *et al*[30] have pointed out that in patients with unresectable or metastatic CRC, the use of drugs such as olaparib or bevacizumab specifically targets proteins that promote cancer cell proliferation, with fewer toxic effects than FOLFOX chemotherapy. This study's results were consistent with previous reports, demonstrating that olaparib combined with bevacizumab was more effective than oxaliplatin, calcium folinate, and 5-fluorouracil chemotherapy for treating advanced CRC. Specifically, this therapy suppressed the homologous recombination defect of tumor genes by repressing PARP protein and tumor angiogenesis, effectively adopted cytotoxic therapy to increase cell killing, improved the efficiency of killing mutant cancer cells[31], and also effectively delayed tumor angiogenesis. For patients with small tumor masses requiring fewer chemotherapy cycles, it dampened the chance of inducing drug resistance, lowered the possibility of CRC cells becoming resistant to olaparib and bevacizumab, enhanced the immune activity after the resection of large tumors, bettered the clinical efficacy from multiple aspects[32], prolonged the patient's life cycle, and also lessened the damage done to the patient's body by the toxic and side effects of chemotherapeutic drugs[33,34]. This treatment method is relatively safer and more efficient.

Furthermore, this study compared the serum-associated indicators and tumor markers between the two groups subjected to different treatment regimens. The findings revealed no remarkable difference in various indicators between the two groups before treatment, while all indicators were effectively boosted subsequent to distinct treatment regimens. Serum VEGF, MMP-9, and COX-2 levels were significantly reduced in the observation group receiving olaparib combined with bevacizumab compared to the control group. Moreover, a more substantial decrease was observed in tumor markers, including HE4, CA125, and CA199 levels, in the observation group compared to the control group. These results provided evidence that olaparib combined with bevacizumab could effectively dampen tumor neovascularization, kill tumor cells, and assist in reducing tumor burden in patients diagnosed with advanced CRC. VEGF, MMP-9, and COX-2 are critical regulators of tumor angiogenesis, cell migration, as well as extracellular matrix degradation, and are typically present at high levels in advanced CRC[35,36]. HE4, an acidic protein tumor marker mainly expressed in epididymis and vas deferens epithelial cells, has been extensively applied in the diagnosis and prognostic evaluation of cancers such as endometrial cancer, ovarian cancer and lung cancer. The latest studies have also found it abnormally elevated in digestive system tumors [37]. CA125 is a heterogeneous mucin-like glycoprotein widely distributed in the mesothelial cell group and is dramatically heightened in patients with ovarian,

cervical, liver, lung, as well as CRC progression[38]. CA199, a glycolipid substance on the cell membrane, belongs to oligosaccharide tumor-correlated antigens and is widely believed to be highly expressed in patients with cholangiocarcinoma, gastric cancer, liver cancer, as well as colon cancer[39]. Here, bevacizumab was harnessed to block VEGF binding to its receptor to impede tumor neovascularization and suppress the formation of type IV collagen and integral membrane-bound protease[40]. Meanwhile, olaparib functioned in blocking base excision repair, specifically killing cancer cells while also repairing DNA damage after chemotherapy to some extent[41], hence impeding serum VEGF, MMP-9, and COX-2 levels and effectively attenuating the profiles of tumor-related markers HE4, CA125 and CA199 in serum[42].

Nonetheless, this study has some limitations that should be acknowledged. Firstly, the retrospective design of the study may have introduced inherent biases. Additionally, all enrolled cases were from the same hospital, and the research outcomes may be affected by the unique practice of the unit. As such, further prospective studies are recommended to validate these findings and fill the gaps.

CONCLUSION

In summary, the combination of olaparib and bevacizumab has superior clinical efficacy compared to the conventional FOLFOX chemotherapy regimen for treating patients with advanced CRC. Specifically, the combination therapy was found to significantly delay disease progression and reduce serum VEGF, MMP-9, and COX-2 levels, as well as tumor marker HE4, CA125, and CA199 levels, while also exhibiting fewer adverse reactions and a high level of safety and reliability. These findings provide valuable insights for targeted therapies in the context of advanced rectal cancer and have significant clinical implications.

ARTICLE HIGHLIGHTS

Research background

Olaparib and bevacizumab are well-established targeted drugs utilized in the treatment of solid tumors in clinical settings. They can exert anti-tumor effects by inhibiting PARP and tumor neovascularization. Advanced colorectal cancer (CRC) has a high degree of malignancy, and conventional surgical treatment and chemotherapy are effective. However, there is a pressing need to identify safe and effective treatments for patients with advanced CRC.

Research motivation

Olaparib combined with bevacizumab in the treatment of advanced CRC has an ideal clinical efficacy.

Research objectives

This study aims to investigate the short-term efficacy, time to progression, safety, and their effects on the serum parameters of olaparib combined with bevacizumab in advanced CRC treatment.

Research methods

Comparisons were made for the assessment of the short-term efficacy, time to progression (TTP), the incidence of adverse reactions, serum-related parameters [vascular endothelial growth factor (VEGF), matrix metalloprotein-9 (MMP-9), cyclooxygenase-2 (COX-2)], and tumor markers [human epididymis protein 4 (HE4), carbohydrate antigen 125 (CA125), carbohydrate antigen 199 (CA199)] levels in patients with advanced CRC treated with classical FOLFOX chemotherapy and olaparib combined with bevacizumab chemotherapy.

Research results

The objective response rate and disease control rate in the observation group were significantly higher than those in the control group, and the median TTP in the observation group was better than that in the control group. After treatment, the serum levels of VEGF, MMP-9, COX-2, HE4, CA125, and CA199 in the observation group were lower than those in the control group, and the total incidence of adverse reactions in the observation group was also lower than that in the control group.

Research conclusions

Olaparib combined with bevacizumab in the treatment of advanced CRC has a remarkable clinical effect. Specifically, the combination can delay the disease and reduce serum VEGF, MMP-9, and COX-2 levels and tumor markers HE4, CA125, and CA199 levels, with a high degree of safety and reliability.

Research perspectives

The mechanism of olaparib combined with bevacizumab in the treatment of advanced CRC can be further investigated so as to enable a better understanding of its target and provide a comprehensive theoretical basis and data support for the clinical application of this treatment modality in patients with advanced CRC.

FOOTNOTES

Author contributions: Jiang YL drafted the manuscript; Jiang YL and Fu XY collected and analyzed the clinical data; Yin ZH designed the study, reviewed and revised the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of The First Affiliated Hospital, Hengyang Medical School, University of South China.

Informed consent statement: The data used in this study were not involved in the patients' private information, so the informed consent was waived by the Ethics Committee of The First Affiliated Hospital, Hengyang Medical School, University of South China. All patient data obtained, recorded and managed are only used for this study, and all patient information is strictly confidential, without any harm to the patient.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Zhao S

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