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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 one of the most common malignant tumors of the digestive tract across the world, with high morbidity, mortality rate and insignificant early 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. Patients can lose their lives in a short period if no interventions were given in time. Currently, Olaparib and bevacizumab are widely used drugs for the treatment of colon cancer. This study aims to analyze the clinical efficacy of olaparib combined with bevacizumab in the treatment of advanced CRC, hoping to provide ideas for the treatment of advanced CRC.

AIM

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

METHODS

A total of 82 patients with advanced colon cancer admitted to the First Affiliated Hospital of University of South China from January 2018 to October 2019 were retrospectively analyzed. Among them, 43 patients treated with classical FOLFOX chemotherapy regimen were selected as control group, and 39 patients treated with olaparib combined with bevacizumab were selected as observation group. Short-term efficacy, time to progression (TTP) and incidence rate of adverse reactions were compared between the two groups after different regimens. Changes of serum-related indicators (VEGF, MMP-9, COX-2) and tumor markers (HE4, CA125, CA199) levels before and after treatment were compared between the two groups at the same time.

RESULTS

Objective response rate was 82.05% and disease control rate was 97.44% in the observation group, which were significantly higher than 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 had statistical significance (log-rank test value = 5.009, $P = 0.025$). Before treatment, there was no significant difference in serum VEGF, MMP-9, COX-2 levels and tumor markers HE4, CA125, CA199 levels between the two groups ($P > 0.05$). After treatment with different regimens, the above indicators in the two groups were significantly improved ($P < 0.05$), and 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 ($P < 0.05$). Compared with 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 significantly lower, and the difference was statistically significant ($P < 0.05$).

CONCLUSION

Olaparib combined with bevacizumab in the treatment of patients with advanced CRC has a significant clinical effect. It can significantly delay disease progression, reduce the serum levels of VEGF, MMP-9, COX-2 and tumor markers HE4, CA125 and CA199. It has fewer adverse reactions, which is safe and reliable.

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

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Core Tip: Colorectal cancer (CRC) lacks obvious symptoms and signs in the early stage, most patients are found in the middle and advanced stage, missed the best time for surgery, and often can only use chemotherapy and targeted therapy and other regimens for intervention. Olaparib and bevacizumab, as common targeted therapies, have excellent therapeutic effects in a variety of solid tumors. In this study, we collected the clinical data of 82 patients with advanced CRC, retrospectively investigated the clinical efficacy and safety of olaparib combined with bevacizumab in the treatment of patients with advanced CRC, and analyzed the effect of this treatment regimen on the serum levels of VEGF, MMP-9, COX-2 and related tumor markers.

INTRODUCTION

Colorectal cancer (CRC) is a malignant tumor disease of the digestive tract arising from the epithelial tissue of the colon or rectal mucosa and is the third most common cancer worldwide, as well as the fourth leading cause of cancer-related death[1-3]. Epidemiological statistics show that as of 2018, there are about 1.8 million new CRC pathologies worldwide, including about 881000 deaths, which are extremely harmful[4]. In the past fifty years, the incidence and mortality of colon cancer have been increasing year by year in young and middle-aged people under 50 years of age, and since 1994,

the incidence has increased by 2% per year in people under 50 years of age, and the incidence of CRC has surged in young individuals[5]. According to different histological types, colon cancer can be divided into three categories: adenocarcinoma, mucinous adenocarcinoma, and undifferentiated carcinoma[6,7]. Early colon cancer clinical symptoms are not obvious, easy to be missed, the disease progresses to the middle and late often manifested as abdominal pain, abdominal distension, diarrhea, hematochezia and other symptoms. About 20%-50% of patients have developed different degrees of distant organ metastasis at the time of diagnosis[8], which seriously affects the survival and prognosis of patients.

At present, the treatment of colon cancer is mostly performed by surgical resection, however, this approach is not suitable for advanced metastatic colon cancer, and patients are clinically treated with chemotherapeutic drugs through first-line targeted chemotherapy drugs such as 5-fluorouracil, oxaliplatin, and olaparib[9,10]. In addition, with the continuous improvement of targeted molecular therapy, treatment modalities targeting vascular endothelial growth factor (VEGF) as well as epidermal growth factor (EGF) receptors have been demonstrated to significantly improve the survival rate of patients with advanced colon cancer[11,12]. Bevacizumab, as an anti-angiogenic targeted therapeutic agent, has strong anti-tumor activity and has been gradually 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]. However, the effect of olaparib combined with bevacizumab in the clinical treatment of patients with advanced colon cancer is still unclear. Based on this, 82 patients with advanced CRC admitted to the First Affiliated Hospital of University of South China were collected for retrospective analysis in this study in order to investigate the efficacy of olaparib combined with bevacizumab in the treatment of advanced CRC, hoping to provide more effective data support for the application of this treatment regimen in the clinical treatment of advanced CRC.

MATERIALS AND METHODS

General information

Eighty-two patients with advanced colon cancer admitted to the First Affiliated Hospital of University of South China from January 2018 to October 2019 were retrospectively collected as the subjects of this study, including 43 patients treated with classical FOLFOX chemotherapy regimen as the control group and 39 patients treated with olaparib combined with bevacizumab as the observation group, and the control group consisted of 24 males and 19 females; the age ranged from 22 to 71 years, with an average age of (46.02 ± 7.28) years. In the observation group, there were 19 males and 20 females, aged 21-73 years, with a mean age of (48.37 ± 6.41) years. There was no significant 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 that the two groups were comparable.

Inclusion and exclusion criteria

Inclusion criteria: Aged 18 years old or older; diagnosed as advanced colon cancer by magnetic resonance imaging, computed tomography and other imaging examinations combined with pathological section, cytological examination and clinical diagnosis, and all of them are stage III-IV as indicated in the eighth edition of the American Joint Committee on Cancer Cancer Staging Manual[15]; there is at least one objective measurable tumor lesion; blood routine, electrocardiogram and other biochemical tests before treatment are normal; there is no history of drug allergy; clinical data are complete.

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; Expected survival of less than 3 mo.

Treatment regimen

In the control group, 43 patients were treated with classical FOLFOX chemotherapy regimen: oxaliplatin (manufacturer: Zhejiang Hisun Pharmaceutical Co., Ltd.; approval number: GYZZ H20093487): 135 mg/m² intravenous drip for 2 h d1. Calcium folinate (manufacturer: Jiangsu Hengrui Medicine Co., Ltd.; approval number: GYZZ H20000418): 200 mg/m² ivgtt for 2 h d1-3. 5-fluorouracil (manufacturer: Hainan Zhuotai Pharmaceutical Co., Ltd.; approval number: GYZZ H20051626): 2600 mg/m² continuous intravenous pump for 46-48 h. Every 3 wk for 6 cycles of chemotherapy.

Thirty-nine patients in the observation group were treated with olaparib combined with bevacizumab: olaparib (manufacturer: AstraZeneca; registration certificate number: H20180049): 200 mg/time, orally, twice a day, once in the morning and once in the evening. Bevacizumab injection (manufacturer: Shanghai Roche Pharmaceutical Co., Ltd.; approval No.: S20120068): 15 mg/kg intravenous injection 0.5-1 h d1. Every 3 wk for 6 cycles of chemotherapy.

Clinical assay items

Short-term efficacy: According to the iRECIST response evaluation criteria for cancer immunotherapy[16], the efficacy of the two groups of patients was evaluated after the end of treatment, and the short-term efficacy was divided into complete response (iCR), partial response (iPR), stable disease (iSD) and progressive immune disease (iPD). Among them, iCR is regarded as the tumor changes basically disappear, the clinical symptoms are improved, iPR is regarded as the tumor volume is significantly less, and no new tumor metastasis or lesion occurs, iSD is regarded as the tumor volume is reduced, but the degree of reduction is less than 25%, but no new metastasis or lesion occurs, iPD is regarded as the tumor volume is not significantly changed, and the number of distant metastasis and lesion increases 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 in the two groups during the follow-up period, in which the non-progression and survivors were considered censored data after the end of the follow-up.

Serum-related parameters: 5 mL fasting venous blood was drawn from the patients in the two groups before the start of treatment and after 6 cycles of treatment, and the serum was separated after high-speed centrifugation and stored in an ultra-low temperature freezer at −80 ℃ for later use. Serum VEGF, MMP-9, and COX-2 levels were measured by enzyme-linked immunosorbent assay[17]. VEGF kits were purchased from Beijing Zhongshan Biotechnology Co., Ltd., MMP-9 kits were purchased from Anhui Anke Biological Co., Ltd., and COX-2 kits were purchased from Shanghai Kaibo Biochemical Reagent Co., Ltd. All operations were performed in strict accordance with the kit instructions.

Tumor markers: 5 mL fasting venous blood was collected from patients in the two groups before the start of treatment and after 6 cycles of treatment, and serum was separated after high-speed centrifugation and stored in an ultra-low temperature freezer at −80 ℃ for later use. The levels of tumor markers HE4, CA125 and CA199 in serum samples were measured by enzyme-linked immunosorbent assay[18] using 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 performed in strict accordance with the kit instructions.

Adverse reactions: Close observation, statistics and recording of gastrointestinal reactions, thrombosis, bone marrow suppression and liver and kidney function injury and other adverse reactions and symptoms in the two groups, and calculate the incidence.

Statistical analysis

SPSS 22.0 software was used to process and analyze all data in this study. Measurement data were expressed as (mean ± SD). *t* test was used. Enumeration data were expressed as percentage. χ^2 test was used. Kaplan-Meier was used to calculate the TTP. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of short-term efficacy between the two groups

The short-term efficacy was compared between the two groups after treatment with different regimens. The results showed that ORR was 82.05% and DCR was 97.44% in the observation group, which were significantly higher than 58.14% and 83.72% in the control group. As shown in Table 2, there was a significant difference in the short-term efficacy between the two groups ($P < 0.05$).

Comparison of time to disease progression between the two groups

Kaplan-Meier analysis showed 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 significantly better than that in the control group (Figure 1), and the difference was statistically significant (log-rank test value = 5.009, $P = 0.025$).

Comparison of serum-related index levels between the two groups

Before treatment, there was no significant difference in serum VEGF, MMP-9 and COX-2 levels between the two groups ($P > 0.05$). After treatment with different regimens, the above indicators were significantly improved in the two 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, which were lower than those in the control group (375.60 ± 22.05) pg/mL, (256.78 ± 17.62) mg/L and (523.41 ± 27.48) ng/L (Table 3), and the difference had statistical significance ($P < 0.05$).

Comparison of tumor marker levels between the two groups

Before treatment, there was no significant difference in the levels of tumor markers HE4, CA125 and CA199 between the two groups ($P > 0.05$). After treatment with different regimens, the above indicators in the two groups were significantly improved ($P < 0.05$). 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, which were lower than those in the control group (184.65 ± 22.34) pmol/L, (58.56 ± 6.08) ng/mL and (82.84 ± 9.28) U/mL (Table 4), and the difference had statistical significance ($P < 0.05$).

Comparison of the incidence of adverse reactions between the two groups

Compared with the control group, the total incidence rate of gastrointestinal reactions, thrombosis, bone marrow suppression, liver and kidney function injury and other adverse reactions in the observation group was 5.12%, significantly lower than 20.94% in the control group, and the difference was statistically significant ($P < 0.05$), as shown in Table 5. The adverse reactions experienced by patients in both groups were relieved after receiving timely symptomatic treatment, which had no significant effect on the implementation of this treatment plan.

DISCUSSION

Global cancer incidence and mortality statistics indicate that colon cancer has become the second most common cancer worldwide, after lung cancer, with an incidence as high as 10.2% and a mortality rate of 9.2%[19]. CRC has no obvious specific symptoms in the early stage, and is mostly screened out in routine health examinations. Most patients with CRC are found when they seek medical treatment for hematochezia, diarrhea, abdominal pain, weight loss, anemia and weight loss. At this time, patients are basically in the middle and advanced stage. Tumor lesions and metastases consume the patient's body seriously, and invasive surgical resection or treatment methods with greater toxicity and side effects are not suitable for advanced patients[20,21]. Therefore, it is of great significance to explore an effective treatment plan for advanced CRC to prolong the patient's life cycle and improve the quality of life.

The early treatment of colon cancer is mainly surgical resection of tumor lesions, for advanced colon cancer, high degree of malignancy and strong metastasis are the difficulties of its clinical treatment[22,23]. Moghadamyeghaneh *et al*[24] found in a survey of 7786 patients who underwent resection of colon cancer that approximately 10.8% of patients developed metastases at the time of surgery, and patients with metastatic colon cancer had significantly higher postoperative morbidity and mortality than patients with localized colon cancer. At present, for the treatment of patients with 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, and the effect is good in clinical practice, which can significantly improve the progression-free survival and overall survival rate of patients[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 tumor markers HE4, CA125, and CA199 Levels before and after treatment in patients with advanced colon cancer treated with the standard FOLFOX chemotherapy regimen of 5-fluorouracil, oxaliplatin, and Calcium Folinate combination, and the chemotherapy regimen using olaparib combined with bevacizumab.

In this study, 43 patients in the control group treated with standard FOLFOX chemotherapy regimen and 39 patients in the observation group treated with olaparib combined with bevacizumab chemotherapy regimen were retrospectively analyzed to compare the clinical efficacy, disease progression time and adverse reactions between the two regimens in the treatment of advanced CRC. The results showed that the ORR and DCR in the observation group were significantly 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 significantly lower than that in the control group, indicating that olaparib combined with bevacizumab in the treatment of advanced CRC patients not only had excellent short-term efficacy, but also significantly prolonged the disease progression of patients, and had lower toxic and side effects.

Compared with the classical FOLFOX chemotherapy regimen, the clinical efficacy was better, and it was safer and more reliable. FOLFOX chemotherapy regimen is a common regimen for the clinical treatment of CRC, but it is easy to cause bone marrow suppression, digestive system and nervous system reactions in patients during clinical application, with greater side effects[28]. In addition, it has also been reported that about 60% of CRC patients do not respond significantly to FOLFOX treatment regimen[29]. Kim *et al*[30] 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 less toxic effects than FOLFOX chemotherapy regimens. This study also shows similar findings. Compared with the control group treated with oxaliplatin, Calcium Folinate and 5-fluorouracil chemotherapy, the use of olaparib combined with bevacizumab inhibited the homologous recombination defect of tumor gene by inhibiting PARP protein and tumor angiogenesis, effectively used cytotoxic therapy to increase cell killing, improve the efficiency of killing mutant cancer cells[31], and also effectively delayed the rate of tumor angiogenesis. For patients with small tumor masses requiring less chemotherapy cycles, it inhibited the chance of inducing drug resistance, reduced the possibility of CRC cells becoming resistant to olaparib and bevacizumab, enhanced the immune activity after resection of large tumors, overall improved the clinical efficacy from multiple aspects[32], prolonged the patient's life cycle, and also reduced the damage caused to the patient 's body by the toxic and side effects of chemotherapeutic drugs[33,34]. This treatment regimen is relatively safer and more efficient.

In addition, this study also compared the serum-related indicators and tumor markers between the two groups using different treatment regimens. The results showed that there was no significant difference in various indicators between the two groups before treatment, while all indicators were effectively improved after treatment with different regimens. The serum VEGF, MMP-9 and COX-2 Levels in the observation group using olaparib combined with bevacizumab decreased more than those in the control group, while the tumor markers HE4, CA125 and CA199 Levels also decreased

more significantly than those in the control group, which indicated that olaparib combined with bevacizumab in the treatment of patients with advanced CRC could effectively inhibit tumor neovascularization, kill tumor cells and help reduce tumor burden. 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, as an acidic protein tumor marker, is mainly expressed in epididymis and vas deferens epithelial cells, and has previously been commonly used in the diagnosis and prognostic evaluation of cancers such as endometrial cancer, ovarian cancer and lung cancer, and has also been found to be abnormally elevated in digestive system tumors by the latest studies[37]. CA125 is a heterogeneous mucin-like glycoprotein that is widely distributed in the mesothelial cell group and is substantially elevated in patients with ovarian, cervical, liver, lung, as well as CRC progression[38]. CA199 is a glycolipid substance on the cell membrane, which belongs to oligosaccharide tumor-associated antigens and is widely confirmed to be highly expressed in patients with cholangiocarcinoma, gastric cancer, liver cancer, as well as colon cancer[39]. In this study, bevacizumab was used to block VEGF binding to its receptor to inhibit tumor neovascularization, inhibit the formation of type IV collagen and integral membrane-bound protease[40]. At the same time, olaparib plays a role in blocking base excision repair, specifically killing cancer cells while also repairing DNA damage after chemotherapy to some extent[41], overall inhibiting serum VEGF, MMP-9 and COX-2 Levels, and effectively reducing the expression of tumor-related markers HE4, CA125 and CA199 in serum[42].

However, this study also has some limitations, for example, this is a retrospective study, the retrospective nature will inevitably bias the study, and all enrolled cases are from the same hospital, and the article results may be affected by the unique practice of the unit. Further prospective studies will be considered to fill the gaps.

CONCLUSION

In summary, compared with the classical FOLFOX chemotherapy regimen, olaparib combined with bevacizumab has better clinical efficacy in the treatment of patients with advanced CRC, can significantly delay the time of disease progression, reduce the serum VEGF, MMP-9, COX-2 Levels and tumor markers HE4, CA125, CA199 levels, and has fewer adverse reactions, safe and reliable. This retrospective study provides more ideas for targeted therapy of advanced rectal cancer, which is worthy of clinical reference.

ARTICLE HIGHLIGHTS

Research background

Olaparib and bevacizumab are commonly used targeted drugs for the treatment of solid tumors in clinical practice and can exert anti-tumor effects by inhibiting PARP and tumor neovascularization. Advanced colorectal cancer (CRC) has a high degree of malignancy, conventional surgical treatment and chemotherapy are effective, and it is urgent to find a safe and effective treatment for advanced CRC.

Research motivation

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

Research objectives

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

Research methods

To compare the short-term efficacy, time to progression (TTP), incidence of adverse reactions, serum-related parameters (VEGF, MMP-9, COX-2) and tumor markers (HE4,

CA125, CA199) levels in patients with advanced CRC treated with classical FOLFOX chemotherapy and olaparib combined with bevacizumab chemotherapy.

Research results

Objective response rate and disease control rate in the observation group were significantly higher than those in the control group, and median TTP in the observation group was significantly 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 significantly lower than that in the control group.

Research conclusions

Olaparib combined with bevacizumab in the treatment of patients with advanced CRC has a significant clinical effect, can significantly delay the disease, reduce serum VEGF, MMP-9, COX-2 Levels and tumor markers HE4, CA125, CA199 Levels, safe and reliable.

Research perspectives

The mechanism of action of olaparib combined with bevacizumab in the treatment of advanced CRC can be further investigated, understand its target, and provide a full range of theoretical basis and data support for the clinical treatment of olaparib combined with bevacizumab in patients with advanced CRC.

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