Clinical Efficacy of Bevacizumab in Conjunction with Oxaliplatin and Capecitabine in Managing Metastatic Colorectal Cancer

J. ZANG, X. ZHANG, QING WANG AND JIANCHEN GAN*

Department of Colorectal Surgery, Tianjin Union Medical Center, Tianjian 300211, China

This study contains clinical efficacy of bevacizumab in conjunction with oxaliplatin and capecitabine in managing metastatic colorectal cancer. The study population consisted of 150 individuals diagnosed with metastatic colorectal cancer who sought medical care at our hospital between May 2020 and May 2022. These participants were randomly assigned to the observation group or the control group, each comprising 75 individuals. The control group received chemotherapy with the capecitabine plus oxaliplatin regimen, while the observation group received bevacizumab in conjunction with the capecitabine plus oxaliplatin regimen. In each treatment cycle, which lasted 21 d, both groups received a total of four cycles of chemotherapy. The evaluation included the determination of the objective response rate, disease control rate, Karnofsky performance status, tumor markers, and adverse reactions in both groups. In terms of the objective response rate (66.67 %) and the disease control rate (94.67 %), the observation group outperformed the control group, whose corresponding rates were 45.33 % and 74.67 % respectively ($p<0.05$). Significant improvements in Karnofsky performance status scores were observed in both groups after treatment, with the observation group exhibiting a more pronounced increase as opposed to the control group ($p<0.05$). In terms of the observed adverse reactions, the observation group displayed a remarkably lower prevalence of fatigue and liver function damage in contrast to the control group. By utilizing a combined treatment of bevacizumab, oxaliplatin, and capecitabine, individuals with metastatic colorectal cancer can experience improvements in their objective response rate and disease control rate, enhancements in their functional status scores, and reductions in the levels of serum tumor markers. The safety profile of the treatment regimen is comparable to, or even superior to the conventional approach, making it a worthwhile candidate for further promotion and application.

Key words: Bevacizumab, oxaliplatin, capecitabine, metastatic colorectal cancer, chemotherapy

The incidence of metastatic Colorectal Cancer (mCRC) has been steadily increasing in recent years, highlighting its recognition as a frequent malignant tumor impacting the gastrointestinal system. With a multifactorial origin and a notable mortality rate, effective strategies to combat mCRC are of utmost importance[1]. Roughly 25 % of colorectal cancer patients are diagnosed during the advanced stages, resulting in missed opportunities for timely surgical intervention. Furthermore, about 50 % of individuals undergoing treatment encounter metastasis, significantly impacting both the subsequent therapeutic approaches and the overall well-being of patients[2]. As the disease progresses, symptoms such as intestinal stenosis, intestinal obstruction, bleeding caused by tumor invasion, and metastasis of cancer cells may occur, requiring systemic chemotherapy to prolong life[3,4]. Serving as a Vascular Endothelial Growth Factor (VEGF) monoclonal antibody, bevacizumab is classified as a targeted therapy medication. Its mechanism of action involves the inhibition of VEGF binding to endothelial cell receptors, displaying remarkable selectivity towards tumor cells and effectively suppressing their growth and spread[5,6]. The utilization of oxaliplatin in the management of mCRC has gained widespread recognition. Functioning as a

***Address for correspondence**
E-mail: gjcscholar@163.com

platinum-based chemotherapy agent, oxaliplatin disrupts cancer cell replication through its interaction with Deoxyribonucleic Acid (DNA), effectively impeding tumor growth. However, it can cause significant damage to liver function[7]. As a novel fluoropyrimidine medication, capecitabine undergoes a metabolic transformation, starting with its conversion into 5-deoxy-5-fluorocytidine in the gastrointestinal tract, followed by its further conversion into fluorouracil within the liver, subsequent to oral administration. It treats the affected areas, promotes apoptosis of colorectal cancer cells, and can reduce cross-resistance to platinum-based drugs[8]. Oxaliplatin and capecitabine are often used in conjunction with bevacizumab. This combination therapy can inhibit tumor cell growth and spread through multiple pathways, while reducing the occurrence of drug resistance. In addition, the combined use of these drugs may improve patient survival rates and enhance their quality of life[9]. However, despite some supporting data from relevant studies on the combined use of bevacizumab with oxaliplatin and capecitabine, there is currently a dearth of large-scale, multicenter clinical trials evaluating its clinical efficacy and safety. Hence, in an endeavor to delve deeper into the possibilities of combined chemotherapy regimens led by bevacizumab for managing mCRC, we carried out a clinical observational study. The overarching aim of this research was to investigate the clinical outcomes and potential adverse reactions pertaining to this therapeutic approach. Within the timeframe of May 2020 to May 2022, a retrospective study was performed at our hospital, examining a group of 150 individuals with mCRC who had been admitted for treatment. The pathologically confirmed mCRC; no allergies to the study drugs and no other treatment received in the month prior to inclusion. The significant adverse reactions to the study drugs or severe organ failure preventing further treatment; concomitant cardiac, hepatic, or renal dysfunctions were excluded. Within the group of 150 individuals, there were 89 males and 61 females, whose ages varied from 37 y to 77 y old. 77 individuals had colon cancer and 73 had rectal cancer. By utilizing a random number table, the patients were assigned to either the control group or the study group, with an equal distribution of 75 patients in each group. The control group was administered with chemotherapy consisting of oxaliplatin and capecitabine, while the study group received bevacizumab in conjunction with oxaliplatin and capecitabine treatment. Among the participants in the control group, 48 were male and 27 were female, with ages ranging from 42 y to 73 y and an average age of (57.6±14.7) y. The distribution of cancer types included 39 cases of colon cancer and 36 cases of rectal cancer. Among the participants in the study group, 25 were male and 14 were female, with ages ranging from 37 y to 77 y and an average age of (55.5±15.2) y. There were 38 cases of colon cancer and 37 cases of rectal cancer. No notable distinctions in gender, age, and disease type were found between the two groups ($p>0.05$), suggesting comparability between them. Ethical clearance was granted by the hospital's ethics committee for this study, ensuring the involvement of patients who provided informed consent and duly completed the required consent forms. The control group received Capecitabine plus Oxaliplatin (XELOX) regimen chemotherapy, which involved intravenous infusion of oxaliplatin (source: Geesmee (Wuhan) Pharmaceuticals Co., Ltd., National Medical Products Administration number H20103184, specification: 50 mg/vial) at a dose of 130 mg/m² on d 1 for 2 h, followed by oral administration of capecitabine tablets (source: Chengdu Yuandong Biological Pharmaceutical Co., Ltd., National Medical Products Administration number H20203570, specification: 0.5 g/tablet) at a dose of 1000 mg/m² twice daily for 14 d, with a 7 d break, constituting one cycle every 21 d. The study group received bevacizumab in combination with the XELOX regimen. The XELOX regimen in the study group mirrored that of the control group, except for the inclusion of an intravenous infusion of bevacizumab injection at a dosage of 7.5 mg/kg of body weight (source: Suzhou SDY BioPharmaceuticals Co., Ltd., National Medical Products Administration number S20210020, specification: 100 mg/vial) on d 1, constituting one cycle every 21 d. Both groups underwent four cycles of chemotherapy, and after completion of chemotherapy, the treatment response was evaluated. Objective Response Rate (ORR) and Disease Control Rate (DCR) after four cycles were compared. And comparison of Karnofsky Performance Status (KPS) scores prior to and following four cycles of treatment in both groups.

The KPS scores vary between 0 and 100, with elevated scores signifying improved physical performance[10]. Comparison of serum tumor marker levels, including Carbohydrate Antigen (CA)-19-9), Carcinoembryonic Antigen (CEA), and CA125, before and after four cycles of treatment in both groups. The incidence of adverse reactions, such as fatigue, liver function impairment, anemia, nausea/vomiting, platelet reduction, and leukopenia, during the treatment period between the two groups were compared. After completion of treatment, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) examinations were performed, and the treatment response was evaluated according to the RECIST 1.1 criteria[11], which classified the results as Complete Response (CR), Partial Response (PR), Stable Disease (SD), or Disease Progression (PD). The ORR was calculated as (CR+PR) divided by the total number of cases, multiplied by 100 %, and the DCR was calculated as (CR+PR+SD) divided by the total number of cases, multiplied by 100 %. Statistical Package for the Social Sciences (SPSS) 25.0 will be utilized to perform the statistical analysis in this research. Continuous variables will be reported as means and standard deviations (x±s) and analyzed using t-tests. Categorical variables will be presented as frequencies and percentages (n (%)) and analyzed using Chi-square (χ^2) tests. To establish statistical significance, a significance level of $p<0.05$ will be employed. Comparing the rates presented in Table 1, it is evident that the observation group exhibited significantly higher ORR (66.67 %) and DCR (94.67 %) as opposed to the control group. The control group had response and control rates of 45.33 % and 74.67 %, respectively, which were considerably lower ($p<0.05$). Prior to treatment commencement, no remarkable disparity in KPS scores was observed between the two groups ($p>0.05$). However, following four treatment cycles, both groups witnessed noteworthy improvements in KPS scores compared to the baseline. Moreover, it is important to highlight that the observation group attained notably higher scores than the control group ($p<0.05$) as shown in Table 2. Prior to initiation of treatment, no notable distinction was observed in the levels of CEA, CA125, and CA19-9 between the two groups ($p>0.05$). Nonetheless, there was a noticeable contrast in the serum tumor marker levels between the two groups post-treatment ($p<0.05$) (Table 3). In Table 4, it can be observed that the occurrence rates of fatigue and liver function impairment in the observation group were notably lesser as opposed to the control group ($p<0.05$). However, no significant variations in the occurrence rates of anemia, nausea/vomiting, platelet reduction, and leukopenia was observed between the two groups ($p>0.05$). Prior to the 1990s, patients with colorectal cancer were predominantly treated with fluorouracil and capecitabine as the mainstay of therapy. However, with the introduction of oxaliplatin in the 1990s, the efficacy of colorectal cancer treatment improved. With the development of molecular biology, targeted therapy has played an important role in managing malignant tumors, including colorectal cancer. Targeted drugs used in the treatment of colorectal cancer mainly include cetuximab, panitumumab, and bevacizumab[12-15]. According to our study results, the administration of bevacizumab in conjunction with the XELOX regimen showed significant advantages in treating individuals with mCRC. There was a notable discrepancy in the ORR between the observation and control groups, with rates of 66.67 % and 45.33 % respectively ($p<0.05$). Moreover, the DCR for the observation group was 94.67 %, compared to 74.67 % for the control group. These data highlight the benefits of utilizing bevacizumab in treating mCRC patients. Additionally, noteworthy improvements were observed in the KPS scores of the observation group following treatment. The KPS scores of the observation group showed a significant increase after treatment, surpassing their pre-treatment scores and significantly exceeding those of the control group, signifying statistically significant differences ($p<0.05$). These findings indicate that the utilization of bevacizumab alongside the XELOX regimen can enhance the overall quality of life and functional status of patients. These findings support the clinical efficacy and potential benefits of bevacizumab in conjunction with the XELOX regimen in managing mCRC. Nevertheless, additional validation through large-scale and multicenter clinical trials is necessary to confirm these findings and evaluate the long-term safety and survival outcomes of this treatment approach. Additionally, future research could explore the molecular mechanisms underlying the effectiveness of bevacizumab and its potential for overcoming

drug resistance in colorectal cancer. Moreover, significant variations ($p<0.05$) in serum tumor marker levels were noted between the observation and control groups after treatment. This indicates that the treatment regimen in the observation group can more effectively inhibit tumor growth and progression, leading to a decrease in serum tumor marker levels, which is consistent with previous reports in the literature[16]. With regards to the occurrence rates of adverse reactions, the observation group demonstrated notable reductions in the rates of fatigue and liver function impairment, which were notably lower when as opposed to those observed in the control group. It can be inferred that the utilization of bevacizumab alongside the XELOX regimen may contribute to a reduction in the occurrence rates of fatigue and liver function impairment. Other types of adverse reactions were similar to those of the traditional XELOX regimen and did not significantly elevate the likelihood of adverse reactions. To summarize, our study findings demonstrate that the incorporation of bevacizumab into the XELOX regimen confers notable clinical benefits for individuals diagnosed with mCRC. Implementation of this strategy has the capacity to improve both ORR and DCR, while also enhancing functional status scores and reducing serum tumor marker levels. Furthermore, its safety profile is comparable to or even better than the traditional regimen. These findings provide a new treatment option for mCRC and are expected to enhance treatment outcomes and elevate patient's life quality. Nevertheless, it is important to acknowledge the limitations of our study, including a limited sample size and a single-center approach. As a result, additional validation of our findings is warranted through multicenter randomized controlled trials.

TABLE 1: COMPARISON OF EFFICIENCY AND CONTROL RATE

Group (n=75)	CR	PR	SD	PD	ORR	DCR
Observation	12 (16.00)	38 (50.67)	21 (28.00)	4 (5.33)	50 (66.67)	71 (94.67)
Control	5 (6.67)	29 (38.67)	22 (42.67)	19 (25.33)	34 (45.33)	56 (74.67)
χ^2			-		6.926	11.554
p			-		0.008	0.001

TABLE 2: COMPARISON OF KPS SCORES

Group (n=75)	KPS		t	p
	Before	After		
Observation	71.03±6.47	84.47±11.14	9.035	0.000
Control	71.96±7.83	77.73±8.67	-4.278	0.000
t	0.796	4.134	-	-
p	0.427	0.000	-	-

TABLE 3: COMPARISON OF TUMOR MARKERS

Group (n=75)	CEA (μg/l)		CA125 (U/ml)		CA199 (U/ml)	
	Before	After	Before	After	Before	After
Observation	8.34±2.63	3.38±0.78	60.62±12.41	26.20±7.53	91.47±13.19	33.99±6.67
Control	8.91±2.53	5.81±1.04	61.88±11.53	40.12±9.42	90.02±13.80	50.61±8.58
t	1.339	16.237	0.646	9.992	0.658	12.764
p	0.182	0.000	0.52	0.000	0.512	0.000

TABLE 4: ADVERSE REACTIONS

Group (n=75)	Lack of strength	Impaired liver function	Anemia	Nausea and vomiting	Thrombocytopenia	Leukopenia
Observation	15 (20.00)	12 (16.00)	22 (29.33)	30 (40.00)	10 (13.33)	16 (21.33)
Control	33 (44.00)	23 (30.67)	21 (28.00)	25 (33.33)	11 (14.67)	15 (20.00)
χ^2	9.926	4.509	0.033	0.718	0.055	0.041
p	0.002	0.034	0.857	0.397	0.814	0.84

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Li S, Hu C, Fan C. Efficacy of bevacizumab combined with first-line chemotherapy in the treatment of advanced metastatic colorectal cancer. Chin Contemporary Med 2019;26(33):4-6.
2. Dyer O, Yang G. Colorectal cancer: Given the rising incidence of young adults, U.S. guidelines urge screening from the age of 45. Chin J Surg 2019;57(3):1-7.
3. Cao D, Zheng Y, Xu H, Ge W, Xu X. Bevacizumab improves survival in metastatic colorectal cancer patients with primary tumor resection: A meta-analysis. Sci Rep 2019;9(1):20326.
4. Gao Y, Gao Y, Zhang Q. Efficacy of XELOX regimen combined with bevacizumab in the treatment of metastatic colorectal cancer. Lab Med Clin 2018;15(5):3.
5. Nie J, Liu X, Wang C. Effect of bevacizumab combined with chemotherapy on the expression of cell proliferation factor in patients with resectable colorectal cancer and its clinical efficacy. Tumor Pharm 2019;5(1):6.
6. Chen H, Xu H, Wu X. Efficacy of bevacizumab combined with capecitabine in the treatment of advanced colorectal cancer. Trauma Crit Care Med 2021;12:45-9.
7. Li J, Zhang Y, Wang Y. Research progress of maintenance therapy for unresectable metastatic colorectal cancer. Med Rev 2019;25(7):5.
8. Zhang P, Zhou J, Yang R. Comparative study on the efficacy and safety of oxaliplatin combined with Tigio and oxaliplatin combined with capecitabine in the treatment of advanced gastric cancer. J Clin Military Med 2020;48(7):3.
9. Liu M, Nianfeng YJ. Observation and nursing of adverse reactions of bevacizumab combined with chemotherapy in the treatment of advanced colorectal cancer. Huaihai Med 2017;35(5):2.
10. Wang S. Application of Karnofsky activity score in nursing care of tumor patients. Diet Health Care 2018;5(26):186.
11. Meng Xi, Lu S, Liang Y. Clinical efficacy and safety of apatinib in patients with platinum-resistant ovarian cancer. Chin J Clin Pharmacol 2022;38(20):5.
12. Zhou M, Wang C. Clinical evaluation of oxaliplatin and irinotecan combined with bevacizumab in the treatment of postoperative recurrent colorectal cancer. Anhui Med 2020;24(10):5.
13. Zhou K, Niobium X, Jing D. Clinical efficacy of bevacizumab combined with oxaliplatin+calcium and folinate+fluorouracil in the treatment of advanced metastatic colon cancer. Chin Pharmacoeconomic 2020;15(5):77-83.
14. Kang H. Clinical effect of bevacizumab combined with chemotherapy on elderly patients with advanced colorectal cancer. Chin Minkang Med 2011;9(31):2.
15. Liu Y. Efficacy of bevacizumab combined with chemotherapy in the treatment of advanced colorectal cancer in the elderly. Mod Drug Appl China 2019;13(8):2.
16. Xie C. Evaluation of the efficacy of bevacizumab combined with capecitabine and oxaliplatin in the treatment of metastatic colorectal cancer. Chin Foreign Med Res 2022;20(15):4.

This article was originally published in a special issue, "New Research Outcomes in Drug and Health Sciences" Indian J Pharm Sci 2023:85(6) Spl Issue "290-294"