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Contents

Monthly Volume 16 Number 10 October 27, 2024

EDITORIAL

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

Contents

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 10 October 27, 2024

Retrospective Study

Observational Study

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 10 October 27, 2024

Contents

LETTER TO THE EDITOR

World Journal of Gastrointestinal Surgery

Monthly Volume 16 Number 10 October 27, 2024

Contents

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ORIGINAL ARTICLE

Randomized Controlled Trial

Clinical evaluation of sintilimab in conjunction with bevacizumab for advanced colorectal cancer with microsatellite stable-type after failure of first-line therapy

Liang Wang, Yong-Zhi Diao, Xin-Fu Ma, Yu-Shuang Luo, Qi-Jing Guo, Xiao-Qian Chen

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Abstract

BACKGROUND

At present, immune checkpoint inhibitors (ICIs) remain the 1st-line therapy method for patients suffering from high microsatellite instability /deficient mismatch repair metastatic colorectal cancer (mCRC). However, ICI treatments demonstrate minimal therapeutic efficacy against microsatellite stable (MSS)/proficient mismatch repair (pMMR) CRC. This is mainly because this type of tumor is a "cold tumor" with almost no lymphocyte infiltration. Anti-angiogenic drugs have been found to improve the immune microenvironment by promoting many immune cells to enter the immune microenvironment, thereby exerting anti-tumor effects.

AIM

To investigate the effects of ICIs combined with bevacizumab monoclonal antibody on tumor immune cells in MSS/pMMR advanced CRC patients with first-line treatment failure.

METHODS

A total of 110 MSS/pMMR patients with advanced CRC after first-line treatment failure in the Affiliated Hospital of Qinghai University were enrolled for a randomized controlled trial. In short, patients in the experimental group (n = 60)

were given sintilimab plus bevacizumab for 4 cycles, and those in the control group (n = 50) patients were treated with FOLFIRI combined with bevacizumab for 4 cycles. The expression levels of cluster of differentiation (CD) 8 (+) T cells, tumor-associated macrophages (TAMs), and cancer-associated fibroblasts (CAFs) were comprehensively evaluated to assess the effects of sintilimab combined with bevacizumab on MSS/pMMR advanced CRC sufferers following failure of 1st-line therapy.

RESULTS

The positive expression rates of CD8 (+) T lymphocytes (30% *vs* 50%), TAMs (23.30% *vs* 60%), and CAFs (23.30% *vs* 50%) before and after treatment in both groups exhibited statistical significance (P < 0.05). Additionally, the therapeutic effects of both groups (partial remission: 26.67% *vs* 10%; objective response rate: 26.70% *vs* 10%) were significantly different (P < 0.05). Although the experimental group showed a higher progression-free survival, median progression-free survival, and disease control rate than the control group, the difference was not statistically significant. Moreover, no significant difference in the occurrence rate of drug-related adverse reactions after treatment between the two groups was found (P > 0.05).

CONCLUSION

ICIs in combination with bevacizumab can not only improve the patient's prognosis but also yield safe and controllable adverse drug reactions in patients suffering from MSS/pMMR advanced CRC after failure to a 1st-line therapy.

Key Words: Immune checkpoint inhibitors; Bevacizumab; Colorectal cancer; Cytotoxic T lymphocytes; Tumor-associated macrophages; Cancer-associated fibroblasts

Core Tip: In this study, immune checkpoint inhibitors (ICIs) in combination with bevacizumab were applied to microsatellite stable (MSS)/proficient mismatch repair (pMMR) colorectal cancer (CRC) patients with first-line treatment failure. It was found that ICIs combined with bevacizumab treatment significantly changed the tumor immune cells compared with the pre-treatment period. Additionally, ICIs combined with bevacizumab not only further improved their clinical efficacy compared with ordinary chemotherapy combined with anti-angiogenic drugs, but also yielded safe and controllable adverse drug reactions, which provided a new option for MSS/pMMR CRC patients experiencing 1st-line treatment failure.

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INTRODUCTION

Colorectal cancer (CRC), a frequently diagnosed malignancy arising from the digestive tract in China, has been reported with a high incidence and death rate. Over 1.9 million global new cases of CRC and around 935000 CRC-related deaths are estimated by the 2020 GLOBOCAN statistics. CRC ranks 3rd in the morbidity and 2nd in the death rate among malignancies, contributing to about 1/10 of the morbidity and death rates of cancer[1,2]. Studies[3,4] have proposed that the second-line treatments after first-line treatment for advanced CRC have low efficacy. Therefore, exploring treatment options for advanced CRC after 1st-line treatment failure is currently still a clinical research hotspot.

At present, immune checkpoint inhibitors (ICIs) represent the 1st-line therapeutic approach for high microsatellite instability/deficient mismatch repair (MSI-H/dMMR) metastatic CRC (mCRC). Yet, ICIs show limited therapeutic efficacy for microsatellite stable (MSS) CRC, which is primarily because MSS CRC is a "cold tumor" with almost no lymphocyte infiltration. However, anti-angiogenic drugs can improve the immune microenvironment by promoting more immune cells to enter the immune microenvironment, thereby exerting anti-tumor effects. The REGONIVO and REGOTORI studies[5,6] have confirmed that ICIs combined with anti-angiogenic drugs are beneficial to MSS advanced CRC patients with repeated treatment failure after third-line therapy. The effects of different combinations of ICIs and anti-angiogenic agents may not be completely the same. However, little has been reported about the outcomes and safety of the aforementioned two agents in combination in MSS mCRC sufferers with 1st-line treatment failure.

Cytotoxic cluster of differentiation (CD) 8 (+) T lymphocytes are the main effector cells in tumor immunity. Studies[7] have shown that patients with high-density tumor antigen-specific CD8 (+) T lymphocytes at the invasive tumor edge are more likely to benefit from treatment with programmed death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitors. Tumor-associated macrophages (TAMs) and cancer-associated fibroblasts (CAFs) are the two main stromal cells

in the tumor microenvironment (TME). Multiple studies[8,9] have evidenced that an increased number of TAMs and CAFs, as well as their interaction, can lead to changes in the tumor immune microenvironment (TIM). This not only enhances their pro-tumor effects but also is closely associated with tumor metastasis and recurrence, affecting the efficacy of ICI treatment. Limited research has been reported on the effects of PD-1/PD-L1 inhibitors in combination with anti-vascular endothelial growth factor (VEGF)/VEGF receptor drugs on tumor immune cells.

In this study, 110 patients with MSS/proficient mismatch repair (MSS/pMMR) advanced CRC who failed first-line treatment were prospectively collected, with 60 patients in the experimental group receiving bevacizumab combined with sintilimab treatment for 4 cycles, and 50 patients in the control group receiving FOLFIRI combined with bevacizumab treatment for 4 cycles. The toxic side effects in both groups were observed, and the changes in the number of tumor CD8 (+) T cells, TAMs, and CAFs before and after treatment were analyzed, as well as their correlation with efficacy. The results found that the combination of anti-PD-1 drugs and anti-VEGF drugs can improve the tumor immune tolerance microenvironment of MSS/pMMR advanced CRC and increase the effectiveness of immunotherapy. This study may provide more clinical evidence for future large-sample clinical studies and lay a theoretical foundation for personalized immunotherapy of MSS/pMMR CRC.

MATERIALS AND METHODS

General information

Totally, one hundred and ten patients suffering from MSS/pMMR advanced CRC who had a failure of 1st-line therapy were randomly chosen based on a random number table between October 2021 and June 2023 at the Affiliated Hospital of Qinghai University. Specifically, sixty subjects (36 males and 24 females; aged 50-75 years, mean age = 62.23 ± 7.49 years) were allocated to the experimental group, involving 8 subjects with stage III CRC and 52 subjects with stage IV CRC; 30 subjects with low differentiation tumors, 22 patients with moderate differentiation tumors, and 8 subjects with high differentiation tumors; 36 subjects with colon tumor and 24 subjects with rectal tumor. On the other hand, 50 participants (30 males and 20 females; aged 50-75 years, mean age = 61.20 ± 7.74 years) were allocated to the control group, involving 4 participants with stage III CRC and 46 participants with stage IV CRC; 35 participants with low differentiation tumors, 10 participants with moderate differentiation tumors, and 5 participants with high differentiation tumors; 25 participants with colon tumor and 25 participants with rectal tumor. No statistical difference was found in baseline data between the two groups ($P > 0.05$) (Table 1). This study has been approved by the hospital's Ethics Committee and informed consent has been obtained from the patients.

Inclusion, exclusion, and withdrawal criteria

Inclusion criteria: (1) Patients pathologically confirmed as CRC[10], including signet ring cell carcinoma and mucinous adenocarcinoma meeting the inclusion criteria; (2) Unresectable and regionally advanced or metastatic disease, mutated *RAS* or *BRAF* gene, participants who had experienced 1st-line oxaliplatin plus Bevacizumab and failed 1st-line therapy, no drug history of PD-L1/PD-1 inhibitors; (3) Participants of age between 18-80 years; (4) At least one measurable lesion for imaging evaluation, according to response evaluation criteria in solid tumors[11] criteria; (5) Eastern cooperative oncology group[12] performance status of 0 or 1; (6) Patients with sufficient organ and bone marrow functions; and (7) Patients who signed the written informed consent, and abided by the associated procedures scheduled in the scheme.

Exclusion criteria: (1) Participants previously exposed to any antibody or agents targeting PD-1, PD-L1, PD-L2, CD137, cytotoxic T lymphocyte associate protein-4, or any other antibody or agents specifically targeting T cell co-stimulation or checkpoint pathway; Participants with bone metastasis who are at risk for paraplegia; Participants with wild-type *RAS*/*BRAF* gene; (2) Patients with manifestations of active hemorrhage in known lesions (like hematemesis and melena in the past 2 weeks at random); A gastrointestinal bleeding event of grade 3 or above (national cancer institute common terminology criteria for adverse events v5.0)[13] requiring blood transfusion or invasive intervention or hospitalization in the first 3 months; Severe hemorrhagic diseases, or other conditions that lead to high risk of bleeding; (3) Patients with significant malnutrition[14]; (4) Patients who received attenuated live vaccines within 4 weeks before randomization or planned to receive them during the study; With acute or chronic active hepatitis B virus or acute or chronic active hepatitis C virus infection, active pulmonary tuberculosis, active syphilis infection requiring treatment, and history of primary immunodeficiency; (5) Patients with a history of deep vein thrombosis, pulmonary embolism, or any other serious thromboembolic event within 3 months before randomization (thrombosis related to implantable venous access devices or catheter-related thrombosis, or superficial vein thrombosis were not considered "serious" thromboembolic events); (6) Patients who received anticoagulant therapy; (7) Patients with known or suspected, or a history of autoimmune disorders over the last two years; (8) Sufferers who had a known history of allogeneic organ transplantation and allogeneic hematopoietic stem cell transplantation; and (9) Pregnant (positive pregnancy test in urine or serum) or lactating female patients.

Criteria for withdrawal: (1) Severe toxicity or intolerance to treatment (adverse events)[13]; Participants who self-requested to withdraw from the research; or (2) Participants whom the researcher deemed medically necessary to withdraw from this study.

Methods

Patients in the control group received a treatment regimen of FOLFIRI combined with bevacizumab. On day 1 of each

Table 1 Comparison of baseline data between the two groups, *n* (%)

Characteristic	Experimental group (*n* = 60)	Control group (*n* = 50)	*P* value
Gender			1.000
Male	36 (60.00)	30 (60.00)	
Female	24 (40.00)	20 (40.00)	
Age (years)	62.23 ± 7.49	61.20 ± 7.74	0.480
Clinical stage			0.366
Stage III	8 (13.30)	4 (8.00)	
Stage IV	52 (86.70)	46 (92.00)	
Stage IV			0.532
Hepatic metastases	48 (80.00)	43 (86.00)	
Bone metastases	3 (5.00)	1 (1.66)	
Pulmonary metastasis	1 (1.66)	1 (1.66)	
Brain metastases	0 (0.00)	1 (1.66)	
Degree of differentiation			0.091
Low differentiation	30 (50.00)	35 (70.00)	
Moderate differentiation	22 (36.70)	10 (20.00)	
High differentiation	8 (13.30)	5 (10.00)	
BMI (kg/m^2)	20.58 ± 2.03	20.17 ± 1.65	0.256
Colon tumor	36 (60.00)	25 (50.00)	0.293
Rectal tumor	24 (40.00)	25 (50.00)	

BMI: Body mass index.

cycle, bevacizumab (4 mL: 100mg; Xinda Biopharmaceutical Company Limited, Suzhou, Zhejiang Province, China) (National drug approval, No. S20200013) was intravenously infused at a daily dose of 5 mg/kg; Irinotecan (5 mL: 0.1 g; Qilu Pharmaceutical Company Limited, Haikou, Hainan Province, China) (National Drug Approval, No. H20084572) was administered at a dose of 180 mg/m^2; Calcium folinate (3 mL: 30 mg, Jiangsu Dahongying Hengshun Pharmaceutical Company Limited) (National Drug Approval, No. H20020609) was administered at a daily dose of 400 mg/m^2; Fluorouracil (10 mL: 0.25 g; Sichuan Huiyu Pharmaceutical Company Limited, China) (National Drug Approval, No. H20223398) was administered at a daily dose of 400 mg/m^2; Fluorouracil (10 mL: 0.25 g; 1200 mg/m^2; Sichuan Huiyu Pharmaceutical) (National Drug Approval, No. H20223398) was infused for more than 48 hours into participants through the chemotherapy micro-infusion pump. Following a 21-day interval, the second therapeutic cycle started, with 4 cycles of treatment in total[15].

Patients in the experimental group received a treatment regimen of bevacizumab combined with sintilimab. Sintilimab (10 mL: 100 mg; Xinda Biopharmaceutical) (National Drug Approval, No. S20180016) was intravenously infused at a daily dose of 200 mg; bevacizumab (4 mL: 100 mg; Xinda Biopharmaceutical) (National Drug Approval, No. S20200013) was intravenously infused at a daily dose of 7.5 mg/kg. The infusion time on the first day was controlled at 60-90 minutes, and the subsequent infusions could be controlled at 30-45 minutes. Each cycle lasted for 3 weeks, with 4 cycles of treatment in total[16].

Observation indicators

(1) Main endpoint indicators: Progression-free survival (PFS) and median PFS (mPFS); (2) Secondary endpoint indicators: Indicators for evaluating the efficacy of treatments in two groups according to the relevant efficacy evaluation criteria, specifically including complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR), and disease control rate (DCR); (3) Exploratory endpoint indicators: Indicators for analyzing the impact of ICIs combined with anti-angiogenic drugs on the expression of CD8 (+) T cells, TAMs, and CAFs in the TME; and (4) Safety evaluation: For evaluating drug-related adverse reactions.

Detection of the expression of CD8 (+) T cells, TAMs, and CAFs through immunohistochemistry results

Immunohistochemistry results interpretation: (1) CD8 positive expression localization was analyzed. It's expressed on the membrane of lymphocytes. Observation and scoring of staining intensity: 0 point (no staining), 1 point (light yellow), 2 points (brown-yellow), and 3 points (brown); Observation and scoring of the staining area (counting the stained

lymphocytes in the field of vision): 0 point (< 5% lymphocytes stained), 1 point (5%-25% lymphocytes stained), 2 points (25%-50% lymphocytes stained), and 3 points (> 50% lymphocytes stained). Multiplication of the aforementioned two scores: A product < 2 points was indicative of negative expression; A product ≥ 2 points was indicative of positive expression; (2) CAF expression positioning was conducted. CAF-specific protein, α-smooth muscle actin (α-SMA), was chosen to be the immunoenzyme target antigen, and CAF was represented by α-SMA-positive cells in the tumor stroma. Next, 10 fields of visions (× 400, around 200 cells observed) were chosen to count and score the proportion of positive cells to observed cells: 1 point (≤ 10%), 2 points (10% to 50%), 3 points (50% to 75%), and 4 points (> 75%). Scoring of the staining intensity: 0 point (no staining), 1 point (light yellow), 2 points (brown-yellow), and 3 points (brown). Multiplication of these two scores: 0-3 points (-), 4-5 points (+), 6-7 points (++), and ≥ 8 points (+++), where +, ++, and +++ were deemed positive; and (3) TAM expression positioning was conducted. The region showing the highest immune response in the organization was chosen for quantification, and the immunoreactive score (IRS) was calculated with staining results scored according to positive cell percentage and staining intensity. Scoring of positive cell percentage: 0 point (unstained), 1 point (< 25%), 2 points (25%-75%), 3 points (> 75%). Scoring of staining intensity: 0 point (negative), 1 point (weak positive), 2 points (moderate positive), and 3 points (strong positive). IRS was calculated: IRS = score for the percentage of positive cells × score for staining intensity. IRS = 0-2 points indicated negative/low expression and IRS = 3-9 points indicated positive/high expression.

Statistical analysis

Statistical product and service solutions 25.0 was employed for data analysis. The measurement data conformed to a normal distribution were represented as the mean ± SD, with comparisons realized using the t or t' test of two independent samples. The skewed measurement data were summarized by M (Q_L-Q_U), with the rank sum test available for comparisons. A χ^2 test or rank sum test was utilized for qualitative data comparisons. Statistical significance was assumed if $P < 0.05$. Graphic statistics were generated with the application of GraphPad Prism 9.00 software.

RESULTS

Pre-treatment and post-treatment positive expression rates of CD8 (+) T lymphocytes, TAMs, and CAFs

In the experimental group, positive expression rate of CD8 (+) T lymphocytes was markedly raised following treatment, with remarkably decreased positive rates of TAMs and CAFs observed simultaneously (Figure 1 and Table 2).

Therapeutic outcomes of the two groups

Post-treatment outcomes were evaluated (Figure 2 and Table 3). No case of CR was found in all participants. Statistically significant differences were noted regarding post-treatment outcome PR between the two groups, with 16 cases in the experimental group (ORR = 26.70%) and 5 cases in the control group (ORR = 10.00%) ($P < 0.05$). Although several patients had SD and PD in both groups, this discrepancy was statistically insignificant ($P > 0.05$). Higher ORR and DCR were detectable in the experimental participants as compared to the controls, yet the DCR-based difference was statistically insignificant ($P > 0.05$). PFS insignificantly differed between the experimental and control groups with a P value of > 0.05. The participants in the experimental group had an mPFS of 5 months while that of the controls was 4 months.

Drug-associated adverse events of the two groups

The post-treatment outcomes (drug-associated adverse events) were evaluated. As depicted in Figure 3 and Table 4, there was no statistically significant difference in the incidence of drug-related adverse reactions (such as hypertension, proteinuria, gastrointestinal perforation, bleeding, arterial thrombosis, thrombocytopenia, pneumonia, nephritis, hepatitis, endocrine disorders, and diarrhea and enteritis between the two groups ($P > 0.05$).

DISCUSSION

For the time being, over 50% of CRC cases are diagnosed at the later stage or with distant metastasis. For these patients, chemotherapy alone or in conjunction with molecule-targeted therapy remain the main clinical treatments. Despite the clinical benefits of these treatments for patients[3,4,17-19], considerable limitations exist in the survival improvement. For instance, the patients who suffer from advanced CRC with a previous history of 2nd-line therapy have varying extents of decreased tolerance to chemotherapy, especially in the elderly and frail, with a more obvious accumulation of chemotherapy drug toxicity and complications. Therefore, it is still of great importance in clinical practice to continue to explore safer and more effective treatment options for advanced CRC patients who have failed first-line treatment[20].

Breakthrough progress has been made in the first-line treatment of MSI-H/dMMR mCRC through the application of ICIs. The KEYNOTE-177 study[21] has evaluated the efficacy of pembrolizumab compared to standard treatment (chemotherapy ± bevacizumab or cetuximab) as the first-line treatment for MSI-H/dMMR mCRC patients, and the results show that mPFS is extended from 8.2 months to 16.5 months. The CheckMate142 study[22] has included a total of 45 previously untreated mCRC patients who received treatment with nivolumab 3 mg/kg every two weeks + low-dose ipilimumab 1mg/kg every six weeks, with an ORR of 69%, CR of 13%, 2-year PFS rate of 74%, and 2-year OS rate of 79%. Immune monotherapy or dual immune combination has become a new first-line standard treatment for MSI-H mCRC. However, immunotherapy is almost ineffective for MSS CRC, because these tumors are deemed "cold tumors" that have

Table 2 Pre-treatment and post-treatment positive expression rates of cluster of differentiation 8 (+) T lymphocytes, tumor-associated macrophages, and cancer-associated fibroblasts in experimental participants and controls, *n* (%)

Characteristic	Experimental group (*n* = 60)	Control group (*n* = 50)	*P* value
CD8 (+) T lymphocytes			
Pre-treatment	6 (10.00)	10 (20.00)	0.139
Post-treatment	30 (50.00)	15 (30.00)	0.033
TAMs			
Pre-treatment	46 (76.70)	40 (80.00)	0.673
Post-treatment	14 (23.30)	30 (60.00)	0.001
CAFs			
Pre-treatment	42 (70.00)	35 (70.00)	1.000
Post-treatment	14 (23.30)	25 (50.00)	0.003

CAFs: Cancer-associated fibroblasts; CD: Cluster of differentiation; TAMs: Tumor-associated macrophages.

Table 3 Therapeutic outcomes of the experimental participants and controls, *n* (%)

Characteristic	Experimental group (*n* = 60)	Control group (*n* = 50)	*P* value
CR	0	0	-
PR	16	5	0.023
SD	12	10	1.000
PD	32	35	0.073
ORR	16 (26.70)	5 (10.00)	0.023
DCR	28 (46.70)	15 (30.00)	0.073
PFS (months, mean ± SD)	5.04 ± 1.83	4.69 ± 1.30	0.247
mPFS (months)	5	4	-

CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate; PFS: Progression-free survival; mPFS: Median progression-free survival.

very little lymphocyte infiltration. The transition of "cold tumors" to "hot tumors" will largely improve the immunotherapeutic outcomes. It has been shown that tumor growth and invasion rely on the formation of blood vessels[23]. Moreover, Folkman[24] has proposed an important connection between solid tumors and capillaries; after the formation of solid tumors, they induce endothelial cell proliferation in the surrounding blood vessels, resulting in the formation of new capillaries. Meanwhile, most solid tumors will stop growing in the absence of newly formed capillaries, illustrating the importance of new capillaries in the growth of solid tumors. Additionally, Brem *et al*[25] have also confirmed that the invasion of solid tumors depends on the presence of neovascularization. The results of this study demonstrated that the application of bevacizumab can specifically bind to vascular endothelial factors, thus blocking their binding to receptors, which not only affected the generation of new blood vessels but also rendered the degeneration of existing blood vessels, ultimately further inhibiting tumor growth. This antagonistic effect can also normalize blood vessels, thereby increasing the drug delivery rate within the tumor and achieving the goal of controlling further tumor growth. Combined application with chemotherapy can improve the efficacy of chemotherapy. As has been evidenced previously[26,27], there is an important connection between the TIM and tumor angiogenesis. Inhibiting blood vessel formation can improve the TIM and promote more T lymphocytes to infiltrate the tumor, contributing to transforming a "cold tumor" into a "hot tumor", thereby greatly enhancing the effectiveness of immunotherapy. ICIs can induce the normalization of tumor blood vessels[28]. It has been proposed that specifically recognizing and blocking the binding sites of PD-1 and PD-L1 can help restore the immune cells' ability to distinguish tumor cells, thereby enhancing the body's anti-tumor ability[29]. Therefore, ICIs in combination with anti-angiogenic drugs may achieve a synergistic effect in tumor treatment. The REGOTORI study[5], a phase Ib/II clinical trial, aims to assess the safety, tolerability, and preliminary therapeutic efficacy of regorafenib plus toripalimab in cases of MSS mCRC with failure or intolerance to systemic chemotherapy. The present research validated good therapeutic efficacy (ORR = 15.2%; DCR = 36.4%), providing data to support that the combination of anti-angiogenic drugs and immunotherapy can improve immunogenicity in the TME. In the present study, a statistically remarkable difference was noted between the two groups concerning the post-treatment positive

Table 4 The incidence of drug-associated adverse events in experimental and control participants, *n* (%)

Characteristic	Experimental group (*n* = 60)	Control group (*n* = 50)	*P* value
Hypertension	3 (5.00)	0 (0.00)	0.054
I	2 (3.30)	0 (0.00)	
II	1 (1.70)	0 (0.00)	
Proteinuria	4 (6.70)	5 (10.00)	0.526
I	2 (3.35)	3 (6.00)	
II	2 (3.35)	2 (4.00)	
Gastrointestinal perforation	0 (0.00)	0 (0.00)	-
I	0 (0.00)	0 (0.00)	
II	0 (0.00)	0 (0.00)	
Bleeding	1 (1.70)	0 (0.00)	0.269
I	1 (1.70)	0 (0.00)	
II	0 (0.00)	0 (0.00)	
Arterial thrombosis	0 (0.00)	0 (0.00)	-
I	0 (0.00)	0 (0.00)	
II	0 (0.00)	0 (0.00)	
Thrombocytopenia	7 (11.70)	5 (10.00)	0.780
I	3 (5.00)	3 (6.00)	
II	4 (6.70)	2 (4.00)	
Pneumonia, nephritis, hepatitis, and endocrine disorders	0 (0.00)	0 (0.00)	-
I	0 (0.00)	0 (0.00)	
II	0 (0.00)	0 (0.00)	
Diarrhea and enteritis	3 (5.00)	2 (4.00)	0.801
I	2 (3.30)	2 (4.00)	
II	1 (1.70)	0 (0.00)	
Number of cases	18	12	0.525
I	10	8	
II	8	4	

expression rates of different cell subsets. More experimental participants had augmented positive expression rates of CD8 (+) T lymphocytes but diminished positive expression rates of TAMs and CAFs after treatment than the controls. This may be attributed to the improvement of the TIM by the application of anti-angiogenic drugs, which led to more T lymphocytes infiltrating into the tumor and transformed the "cold tumor" immune suppression state into a "hot tumor" immune support state. The combined application of ICI drugs can further enhance the immune cells' ability to distinguish tumor cells, thereby improving the body's anti-tumor ability, reducing tumor growth, infiltration, and metastasis capabilities, and also reducing the positive expression rates of TAMs and CAFs. This may also be the intrinsic reason why the experimental group had higher PFS, mPFS, ORR, and DCR than the control group.

Additionally, drug-associated adverse events were accurately assessed. The severity was graded following the national cancer institute common terminology criteria for adverse events v5.0 criteria. Among all the observed adverse reactions, adverse events in both groups were graded I or II. After symptomatic or supportive treatment, the patient's conditions were significantly improved, with no cases of discontinuation, withdrawal from the study, or death. Statistical analysis demonstrated no significant difference between the two groups of patients in the overall drug reaction rate and the proportions of drug reactions (like hypertension) ($P > 0.05$). These findings indicated that the combination of ICIs and anti-angiogenic drugs can achieve the same clinical safety as conventional chemotherapy combined with anti-angiogenic drugs. These results may provide more options for advanced CRC patients with varying degrees of chemotherapy tolerance, especially for the elderly and frail, with significant chemotherapy drug toxicity accumulation and complications.

It was found from the short-term perspective that deaths occurred in both groups (8 in the experimental group and 11 in the control group). The experimental participants had a survival rate of 86.70%, where 5 deaths were caused by

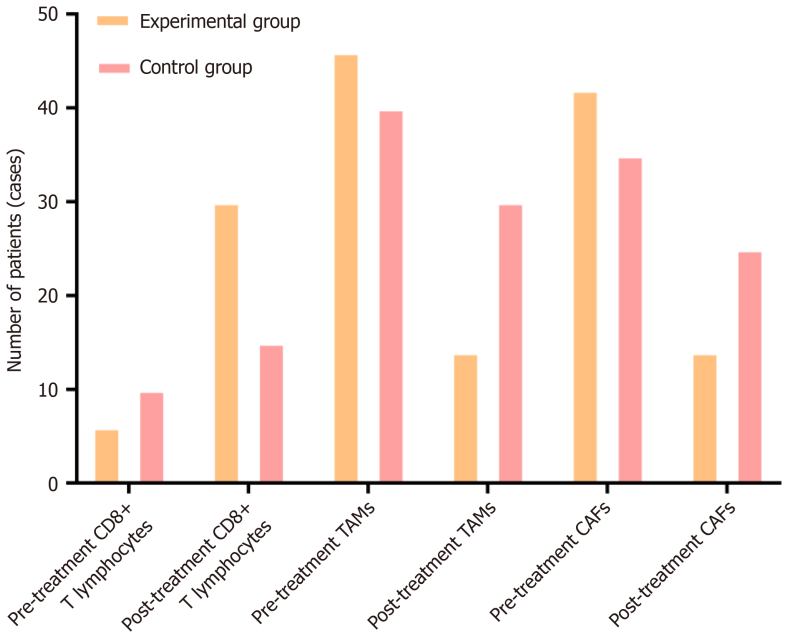

Figure 1 Comparison of the positive expression rates of cluster of differentiation 8 (+) T lymphocytes, tumor-associated macrophages, and cancer-associated fibroblasts before and after treatment in two groups of patients. The percentages of tumor-associated macrophages and cancer-associated fibroblasts in the experimental group were significantly lower after treatment than those before treatment. CD: Cluster of differentiation; TAMs: Tumor-associated macrophages; CAFs: Cancer-associated fibroblasts.

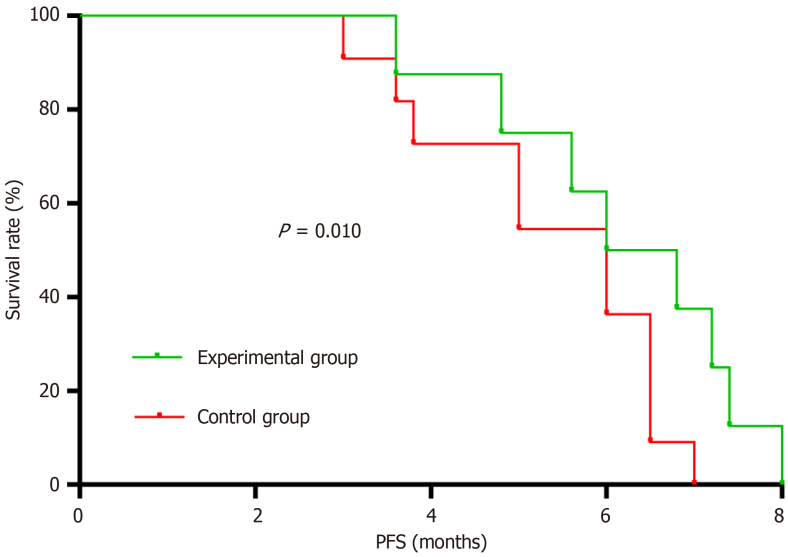

Figure 2 Comparison of short-term survival stations between the two groups. The progression-free survival of the experimental participants was markedly prolonged relative to the controls. PFS: Progression-free survival.

cachexia and 3 deaths were attributed to hepatic failure owing to hepatic metastasis. On the other hand, the controls (a survival rate of 78.00%) contained 6 deaths resulting from cachexia, 3 deaths ascribed to hepatic metastasis-associated hepatic failure, 1 death owing to severe infection because of delayed therapy for secondary complete intestinal obstruction, and 1 death resulting from brain herniation attributed to brain metastasis. No adverse drug reaction-related deaths were observed in both groups, which further demonstrated the good safety and controllability of the combination of these two drugs. The PFS of the deceased experimental participants was notably extended relative to corresponding controls, indicating that the utilization of ICIs plus anti-angiogenic drugs may restrain the growth, infiltrating, and metastatic abilities of tumors, ultimately resulting in an extension of PFS. Both groups had cases of hepatic metastases from CRC, but the incidence insignificantly differed. However, it is undeniable that hepatic metastasis will attenuate the immunotherapeutic efficacy[30]. The methods overcoming liver immune tolerance mechanisms and associated adverse events warrant in-depth explorations in the following research, so as to allow more benefit for patients with CRC and hepatic metastases from immunotherapy.

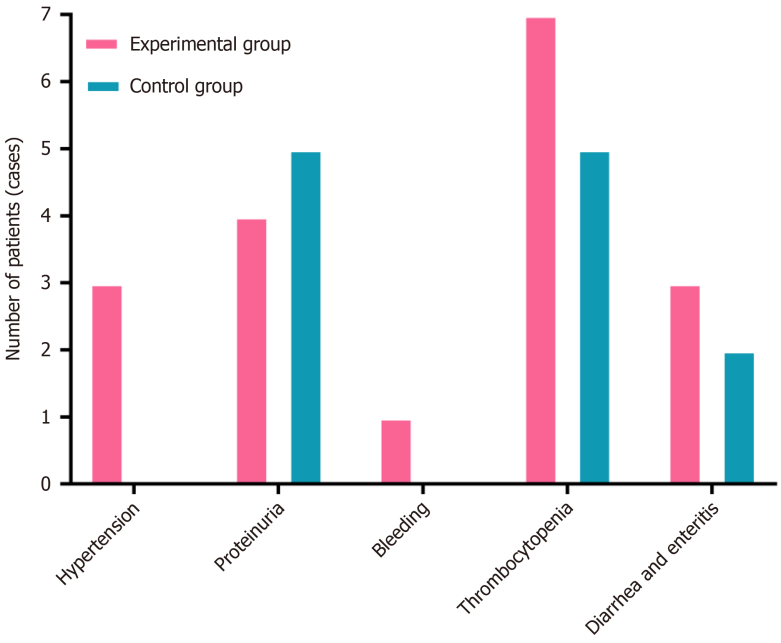

Figure 3 Comparison of drug-related adverse reactions in the two groups of patients. The incidence of adverse events insignificantly differed between experimental participants and controls.

CONCLUSION

The conjunction of ICIs with anti-angiogenic agents improves the TIM of MSS/pMMR advanced CRC patients with failure of 1st-line therapy and meanwhile accelerate the transformation of "cold tumor" immune-suppression condition to a "hot tumor" immune-supportive condition. In consideration of ensured safety of drug adverse reactions, ICIs in conjunction with anti-angiogenic drugs enhance the anti-tumor ability of patients and clinical treatment effects, further increasing its clinical application value. Despite the good results of our research, future combination therapy for tumors should focus more on individualization, multidisciplinary collaboration, and dynamic monitoring. The integration of multiple treatment modalities promotes the formation of more precise and efficient treatment plans to further improve treatment outcomes and reduce toxic side effects. Moreover, it can further improve patient's survival rates and life quality, bringing hope and recovery opportunities to more patients.

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FOOTNOTES

Author contributions: Chen XQ contributed to the study concept and design, revised and reviewed the manuscript; Wang L and Diao YZ co-wrote the manuscript, sharing the first authorship; Ma XF collected the data and reviewed the literature; Wang L was responsible for the data analysis and making figure; Guo QJ was responsible for the experimental operation; Luo YS contributed to the study concept; Chen XQ is the guarantor of this study; All authors contributed to the article and approved the submitted version.

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