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Retrospective Study

Application of sintilimab combined with anlotinib hydrochloride in the clinical treatment of microsatellite stable colorectal cancer

Rui Feng, De-Xin Cheng, Xiao-Chen Chen, Liu Yang, Hao Wu

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Rui Feng, De-Xin Cheng, Department of Interventional Medicine, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Xiao-Chen Chen, Liu Yang, Cancer Center, Department of Radiation Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Hao Wu, Department of Vascular Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Hao Wu, MM, Attending Doctor, Department of Vascular Surgery, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, No. 158 Shangtang Road, Hangzhou 310000, Zhejiang Province, China. wuhao89899@163.com

Abstract

BACKGROUND

Microsatellite stable (MSS) colorectal cancer (CRC) is a common type of tumor with limited treatment options. Sintilimab and anlotinib hydrochloride are two extensively studied anticancer drugs.

AIM

To probe the clinical value of combining sintilimab with anlotinib hydrochloride in MSS CRC treatment.

METHODS

During the period spanning from April 2019 to April 2022, Zhejiang Provincial People's Hospital accommodated a cohort of 92 patients diagnosed with MSS CRC who were classified into two distinct groups in our study, the observation group and the control group. The control group was administered anlotinib hydrochloride as their designated therapy, whereas the observation group received the additional treatment of sintilimab in conjunction with the therapy assigned to the control group. The administration of treatment occurred in cycles consisting of a duration of 3 wk, and the evaluation of effectiveness took place subsequent to the completion of two consecutive cycles of treatment within both groups. A comparative analysis between the two groups was conducted to assess the short-term efficacy and ascertain the incidence of adverse events transpiring throughout the duration of the treatment period. Changes in the levels of carcinoembryonic

antigen, carbohydrate antigen 199 (CA199), CA125, and T cell subsets (CD4+, CD8+, CD4+/CD8+) as well as the assessment of the quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 were compared between the two groups prior to and subsequent to therapy. Finally, a 1-year follow-up was conducted for both groups of patients, and the survival status was recorded and analyzed.

RESULTS

The short-term effectiveness displayed by the observation group surpassed that exhibited by the control group, with a statistically significant discrepancy (76.09% *vs* 50.00%), reaching a significance level denoted as $P < 0.05$. Following the administration of treatment, the observation group manifested a considerable reduction in numerous serum indicators, which were found to be lower than the corresponding pretreatment levels within the same group as well as the post-treatment levels observed in the control group ($P < 0.05$). Post-treatment, the T lymphocyte subset levels within the observation group demonstrated a remarkable amelioration, surpassing the corresponding pre-treatment levels observed within the same group as well as the post-treatment levels observed in the control group ($P < 0.05$). Subsequent to the therapeutic intervention, the observation group showcased a notable amelioration in the scores associated with multiple dimensions of life quality. These scores outperformed the pretreatment scores within the same group as well as the post-treatment scores observed in the control group ($P < 0.05$). The safety levels of drug use in the two group were comparable (19.57% *vs* 13.04%), and no distinct difference was observed upon comparison ($P > 0.05$). After the completion of treatment, both groups of patients underwent a 1-year follow-up outside the hospital. Throughout this period, 1 patient within the observation group and 2 patients within the control group became untraceable and were lost to follow-up. During the follow-up period of the observation group, 12 patients died, resulting in a survival rate of 73.33% (33/45), while in the control group, 21 patients died, resulting in a survival rate of 52.27% (23/44). The implementation of Kaplan-Meier survival analysis revealed a conspicuous contrast in survival rates exhibited by the two groups (log-rank = 4.710, $P = 0.030$).

CONCLUSION

The combination of sintilimab and anlotinib hydrochloride demonstrated favorable efficacy in the treatment of MSS CRC patients, leading to improvements in patient immunity and prognosis. Additionally, it exerted inhibitory effects on the expression of carcinoembryonic antigen, CA199, and CA125.

Key Words: Microsatellite stability; Colorectal cancer; Sintilimab; Anlotinib hydrochloride; Immunity; prognosis

Core Tip: In the treatment of microsatellite stable (MSS) colorectal cancer (CRC), preclinical and early clinical studies have shown that monoclonal antibody therapy and anlotinib hydrochloride has the potential to enhance antitumor immune responses and inhibit tumor growth in MSS CRC. By targeting both the tumor microenvironment and the signaling pathways crucial for cancer cell survival, this dual approach may provide a synergistic effect, leading to improved treatment response and prolonged survival in patients with MSS-CRC. In summary, the combination of monoclonal antibody therapy and hydrochloride anlotinib may offer a new treatment option for patients with MSS CRC.

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INTRODUCTION

Colorectal cancer (CRC) is a frequently encountered malignant tumor affecting the gastrointestinal tract in the realm of clinical practice. Its incidence and mortality rates rank second only to gastric cancer and esophageal cancer among malignant tumors of the digestive system. Typically, patients with CRC do not exhibit typical symptoms at the onset of the disease. However, as the condition progresses, symptoms such as hematochezia and localized abdominal pain may arise, which not only affect patients' normal lives but also pose a threat to their safety[1]. In recent years, owing to shifts in individuals' lifestyles, behaviors, and the escalating prevalence of associated risk factors, there has been a notable surge in the population afflicted by CRC. As a result, the treatment of such patients has garnered widespread attention from various sectors of society. At present, a relatively comprehensive treatment system for CRC has been established in clinical practice, including surgical treatment, radiotherapy, and chemotherapy. Although the efficacy of these treatments has been recognized by many clinicians and patients, clinical studies have unveiled that some patients still have poor responses and unfavorable outcomes[2,3]. Therefore, it is necessary to explore other effective approaches for CRC treatment in clinical settings.

With the advancements in medical technology and the development of immunology and precision medicine, treatment strategies targeting immune therapeutic agents have gradually been applied in the management of malignant tumors[4]. Specifically, immune drugs targeting programmed cell death protein 1 (PD-1) and its ligand (PD-L1) have been employed in clinical settings and have demonstrated favorable outcomes in the treatment of multiple malignancies[5,6]. It is a widely acknowledged fact that approximately 15% of patients diagnosed with CRC manifest the state of microsatellite instability-high (MSI-H) CRC, an entity correlated with malfunctions within the DNA mismatch repair system[7]. Compared to microsatellite stable (MSS) CRC patients, those with microsatellite instability-high CRC tend to have a better response to immune checkpoint inhibitors, such as sintilimab[8]. However, the majority of CRC patients have MSS, and their immune characteristics are predominantly characterized by immune exclusion and immune desert phenotypes, resulting in limited clinical benefits from immune therapy[9]. Therefore, for such patients, a combination approach is often utilized, aiming to improve the immune environment of MSS CRC patients through the combination of immunotherapy with chemotherapy or other local treatment modalities, thereby transforming a "cold" tumor into a "hot" tumor [10].

Anlotinib hydrochloride is an orally administered small molecule tyrosine kinase inhibitor. It selectively suppresses the activity of vascular endothelial growth factor receptor-2, thereby blocking the process of angiogenesis and dampening tumor blood supply, ultimately preventing the formation of new blood vessels[11]. Sintilimab is an immune checkpoint inhibitor that belongs to the PD-1 antibody class. By binding to the PD-1 receptor, it disrupts the interaction between PD-1 and its ligand PD-L1, thus restoring the immune activity of activated T cells against tumor cells[12]. Clinical investigations have substantiated a certain degree of effectiveness attributed to anlotinib hydrochloride and sintilimab in managing malignancies[13]. In an effort to actively explore effective immunotherapy strategies for MSS CRC patients, the primary objective of this study was to undertake the amalgamation of sintilimab with anlotinib hydrochloride as a therapeutic approach for MSS CRC patients and closely monitor the ensuing therapeutic effects. The overarching aim was to contribute valuable insights and guidance for future endeavors pertaining to the treatment of MSS CRC patients.

MATERIALS AND METHODS

Basic data

A total of 92 MSS CRC patients admitted to Zhejiang Provincial People's Hospital from April 2019 to April 2022 were selected as the study subjects. Following a random assignment, the study cohort was segregated into the observation group and the control group, encompassing an equal number of 46 patients in each. The observation group comprised 24 male individuals and 22 female individuals, with a calculated average age of 58.34 ± 3.28 years. Among them, 33 cases (71.74%) had colon cancer, and 13 cases (28.26%) had rectal cancer. Within the study population, a significant majority (41 cases, 89.13%) were identified as having low differentiation, while a smaller subset (5 cases, 10.87%) displayed moderate to high differentiation. Concerning the control group, it consisted of 25 male individuals and 21 female individuals, with an average age of 58.54 ± 3.49 years. Among them, 31 cases (67.39%) had colon cancer, and 15 cases (32.61%) had rectal cancer. There were 37 cases (80.43%) with low differentiation and 7 cases (15.22%) with moderate to high differentiation. There were no substantial statistical variances between the two groups in terms of sex, age, pathological type, differentiation degree, and TNM stage ($P > 0.05$), indicating comparability between the groups. Please refer to Table 1 for details.

Inclusion and exclusion criteria

Inclusion criteria: (1) Previous failure of first-line chemotherapy and confirmed diagnosis of MSS CRC; (2) Presence of at least one measurable lesion; (3) Age between 18 years and 75 years; and (4) Individuals who willingly engaged and provided their voluntary participation in the study were duly requested to sign an informed consent form subsequent to receiving a comprehensive elucidation regarding the study's objectives and methodologies, which was conscientiously provided by the responsible nurse. Exclusion criteria: (1) Previous treatment with immune-targeted drugs; (2) Allergy to the drugs used in this research; (3) Severe cardiac, hepatic, or renal dysfunction; (4) Concurrent blood or immune system disorders; (5) Estimated survival time of fewer than 3 mo according to physician assessment; and (6) Inability of special populations to cooperate with the study, such as cognitive impairment, mental disorders, *etc.*

The present study obtained the endorsement of the Ethics Committee of Zhejiang Provincial People's Hospital and adhered to the guidelines of Good Clinical Practice as stipulated by the International Conference on Harmonization and the principles enshrined in the Declaration of Helsinki. Prior to participation, all patients were provided with comprehensive information and willingly signed informed consent forms.

Methods

Anlotinib hydrochloride (manufactured by Chiatai Tianqing Pharmaceutical Co., Ltd., China, National Drug Approval Number: H20180003, specification: 10mg) was administered as the designated therapeutic intervention for patients assigned to the control group. The medication was administered orally at a dose of 10 mg per dose, once daily. The treatment was given continuously for 2 wk, followed by a 1-wk drug-free period. Three weeks constituted one cycle, and the medication was given for a total of 2 cycles.

In conjunction with the treatment administered to the control group, the patients belonging to the observation group underwent the additional therapeutic regimen involving sintilimab [manufactured by Innovent Biologics (Suzhou) Co., Ltd., China, National Drug Approval Number: S20180016, specification: 100mg: 10 mL/bottle]. A 200 mg dosage of sintilimab injection solution was effectively dissolved in a solution of 0.9% sodium chloride injection. The concentration of the resulting solution was meticulously adjusted within the range of 1.5-4.0 mg/mL, taking into consideration the

Table 1 Comparison of basic data between the two groups

Item		Observation group, *n* = 46	Control group, *n* = 46	χ^2	*P* value
Sex	Male	24 (52.17)	25 (54.35)	0.044	0.834
	Female	22 (47.83)	21 (45.65)		
Age in yr		58.34 ± 3.28	58.54 ± 3.49	0.283	0.778
Pathological type	Colon cancer	33 (71.74)	31 (67.39)	0.205	0.650
	Rectal cancer	13 (28.26)	15 (32.61)		
Differentiation degree	Low differentiation	41 (89.13)	37 (80.43)	0.494	0.482
	Moderate to high differentiation	5 (10.87)	7 (15.22)		
TNM stage	Stage III	34 (73.91)	32 (69.57)	0.215	0.643
	Stage IV	12 (26.09)	14 (30.43)		
Distant metastasis	Hepatic metastasis	2 (4.35)	1 (2.17)	0.000	1.000[1]
	Pulmonary metastasis	1 (2.17)	0 (0.00)	0.000	1.000[1]
	Pelvic metastasis	1 (2.17)	1 (2.17)	0.511	0.475[1]

[1]The use of continuity correction, which is applied in χ^2tests when the expected frequency is less than or equal to 5 to perform a continuity-corrected test. Data are *n* (%) or mean ± SD.

individual patient's tolerance level. The solution was administered intravenously once every 3 wk, with an infusion duration of 30-60 min. The patients received a total of 2 cycles of treatment.

Observation of indicators

Efficacy assessment: Post-treatment evaluations of patients were conducted in accordance with pertinent criteria[14]. A complete response was delineated as the complete vanishing of lesions, persisting for a minimum of 4 wk. On the other hand, a partial response was characterized by a reduction of 30% or more in the cumulative sum of the maximum diameters of lesions, accompanied by the absence of any new lesions, and consistently maintained for a minimum duration of 4 wk. Stable disease was precisely characterized as a reduction of less than 30% or an augmentation of more than 20% in the cumulative sum of the maximum diameters of lesions. In contrast, disease progression was meticulously defined as an escalation of 20% or more in the cumulative sum of the maximum diameters of lesions or the manifestation of new lesions.

Laboratory parameter testing: Carbohydrate antigen 199 (CA199) and CA125 were measured using the Roche Cobase601 fully automated electrochemiluminescence immunoassay system and the corresponding reagent kits produced by Roche Group, Switzerland. Carcinoembryonic antigen (CEA) was gauged *via* enzyme-linked immunosorbent assay, and the enzyme-linked immunosorbent assay kits were provided by Wenzhou Kemiao Biotechnology Co., Ltd. T cell subsets (CD4+ and CD8+) were determined using the FC500 MCL flow cytometer produced by Beckman Coulter, Inc., United States, and the CD4+/CD8+ ratio was calculated.

Quality of life evaluation: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 scale was utilized for assessment[15]. The questionnaire consists of four dimensions: functional domains; symptom domains; general health status/quality of life domains; and individual item measurements. Higher scores in the functional domains and general health status/quality of life domains indicate better quality of life, whereas lower scores in the symptom domains and individual item measurements suggest better quality of life.

Safety assessment: Safety evaluation was conducted in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0[16]. Incidents of adverse events (AEs) transpiring within both patient cohorts were meticulously documented and subjected to comprehensive analysis.

Follow-up: After the completion of treatment, both groups of patients were followed up for 1 year. Follow-up was conducted through telephone or outpatient visits once every 3 mo to monitor patient survival.

Statistical analysis

The data were processed with the assistance of SPSS 22.0 statistical software. The Kolmogorov-Smirnov method was employed to examine the normality of measurement data. Data conforming to a normal distribution were expressed as mean ± SD, while the comparative analysis between the two groups was performed using an independent sample *t*-test. Enumeration data were represented as a percentage, and comparisons between groups were performed using the χ^2 test. Survival curves were derived using the Kaplan-Meier technique, and the log-rank test was utilized. When $P < 0.05$, statistical significance was determined.

RESULTS

Comparison of short-term efficacy

The short-term effectiveness exhibited by the observation group surpassed that demonstrated by the control group, with a noticeable disparity of 76.09% *vs* 50.00% ($P < 0.05$), as shown in Table 2.

Comparison of serum CEA, CA199, and CA125 levels

Before the initiation of treatment, discernible dissimilarities in serum CEA, CA199, and CA125 levels were not apparent between the two groups ($P > 0.05$). Subsequent to the administration of the combined therapy involving sintilimab and anlotinib hydrochloride, the observation group exhibited levels of CEA, CA199, and CA125 as follows, 52.17 ± 7.40 ng/mL, 51.37 ± 10.22 IU/mL, and 69.14 ± 10.09 U/mL, respectively. These values exhibited a remarkable reduction compared to the corresponding levels observed in the control group. A profound statistical significance was observed in terms of the variances ($P < 0.05$), as shown in Table 3.

Comparison of the levels of T lymphocyte subsets

Prior to treatment there were no remarkable differences in the levels of CD4+, CD8+, and CD4+/CD8+ positive cells between the two groups ($P > 0.05$). Following treatment, the T lymphocyte subset levels within the observation group showcased a remarkable enhancement, surpassing those detected within the control group ($P < 0.05$), as shown in Table 4.

Comparison of life quality

Comparisons of the quality of life between the two groups of patients suggested no remarkable differences in the scores of each dimension prior to treatment ($P > 0.05$). Following the completion of treatment, the observation group showcased considerable improvements across all dimensions of the quality of life, with statistically significant alterations noted ($P < 0.05$), as shown in Table 5.

Comparison of AEs

Over the course of the treatment period, the most commonly documented AEs in both the observation and control groups included fever, fatigue, dizziness/headache, reduced appetite, and diarrhea. The collective occurrence rate of AEs within the observation group amounted to 19.57%, failing to exhibit a discernible statistical disparity in comparison to the control group's incidence of 15.22% ($P > 0.05$), as shown in Table 6. Most patients experienced mild to moderate AEs, which were typically observed and resolved on the same day with appropriate management after administration.

Comparison of 1-year survival status

After the completion of treatment, a period of 1 year was allocated for the follow-up of patients in both cohorts. Over the course of this specified timeframe, it came to light that 1 patient from the observation cohort was unable to be tracked for follow-up, whereas 2 patients from the control group experienced the same outcome. Within the observation group, a total of 12 patients passed away during the designated follow-up period, subsequently culminating in a survival rate of 73.33% (33/45). As for the control group, 21 patients passed away during the period of follow-up, culminating in a survival rate of 52.27% (23/44). Kaplan-Meier survival analysis showed a substantial discrepancy in survival rates observed between the two cohorts (log-rank = 4.710, $P = 0.030$). Figure 1 delineates the survival curves for both groups.

DISCUSSION

The occurrence of CRC is inextricably associated with genetics, dietary habits, and the presence of familial polyposis, among other factors. In previous reports, it has been pointed out that by 2018, the number of new cases of CRC worldwide had reached nearly 1.85 million, ranking it as the third most prevalent malignant tumor[17]. Typically, CRC does not present with typical symptoms at its onset, and by the time patients are diagnosed, the disease has already progressed to the middle or late stage. Late-stage patients have more severe conditions, and some may also experience metastasis, missing the opportunity for surgical treatment and developing resistance to chemotherapy. Therefore, in clinical practice, second-line chemotherapy or palliative symptomatic treatment is often employed to control disease progression and prolong patient survival[18]. The remarkable advancements attained in the treatment of malignant tumors, specifically middle and late-stage CRC, have been made possible through the unearthing and subsequent clinical utilization of immune checkpoint inhibitors. These groundbreaking findings have opened up fresh avenues and prospects in the realm of CRC treatment. Sintilimab belongs to the PD-1 class of inhibitors, and anlotinib hydrochloride is also a commonly used anti-tumor drug. Here, sintilimab in combination with anlotinib hydrochloride was taken to treat MSS CRC patients, and the short-term and long-term efficacy was observed.

This study discovered that the observation cohort presented with superior short-term efficacy, and the 1-year survival rate throughout the follow-up period attained 73.33%, higher than the 52.27% observed in the control group. This hints that the combination of sintilimab and anlotinib hydrochloride in the treatment of MSS CRC patients has good short-term and long-term efficacy. Anlotinib hydrochloride is a novel anti-tumor targeted drug that has been applied in clinical practice in recent years and has inhibitory effects on kinases correlated with angiogenesis[19]. It is well known that vascular endothelial growth factors boost vascular endothelial cell proliferation and migration, leading to angiogenesis and augmented vascular permeability, which exacerbate the malignant progression of tumors[20]. Anlotinib

Table 2 Comparison of short-term efficacy

Indicator	Observation group, *n* = 46	Control group, *n* = 46	χ^2	*P* value
Complete response	11 (23.91)	5 (10.87)		
Partial response	24 (52.17)	18 (39.13)		
Stable disease	7 (15.22)	20 (43.48)		
Disease progression	4 (8.70)	3 (6.52)		
Overall response	35 (76.09)	23 (50.00)	6.718	0.010

Data are *n* (%).

Table 3 Comparison of serum carcinoembryonic antigen, carbohydrate antigen 199, and carbohydrate antigen 125 levels

Indicators	Time	Observation group, *n* = 46	Control group, *n* = 46	*t*	*P* value
CEA in ng/mL	Before treatment	119.16 ± 18.54	120.06 ± 18.91	0.230	0.818
	After treatment	52.17 ± 7.40[1]	71.24 ± 10.22[1]	110.250	0.000
CA199 in IU/mL	Before treatment	120.16 ± 20.41	120.55 ± 20.59	0.091	0.928
	After treatment	51.37 ± 10.22[1]	62.47 ± 14.04[1]	4.335	0.000
CA125 in U/mL	Before treatment	247.56 ± 25.47	246.91 ± 25.21	0.123	0.902
	After treatment	69.14 ± 10.09[1]	88.15 ± 14.53[1]	7.288	0.000

[1]Denotes a comparison with the pre-treatment values.
Data are mean ± SD. CA: Carbohydrate antigen; CEA: Carcinoembryonic antigen.

Table 4 Comparison of the levels of T lymphocyte subsets

Indicators	Time	Observation group, *n* = 46	Control group, *n* = 46	*t*	*P* value
CD4+ in %	Before treatment	28.40 ± 2.46	28.35 ± 2.50	0.097	0.923
	After treatment	36.45 ± 5.51[1]	32.21 ± 4.01[1]	4.220	0.000
CD8+ in %	Before treatment	27.26 ± 2.36	27.35 ± 2.47	0.179	0.859
	After treatment	21.32 ± 1.10[1]	24.20 ± 1.54[1]	10.321	0.000
CD4+/CD8+ in %	Before treatment	1.04 ± 0.44	1.03 ± 0.47	0.123	0.902
	After treatment	1.71 ± 0.58[1]	1.33 ± 0.52[1]	3.309	0.001

[1]Denotes a comparison with the pretreatment values. Data are mean ± SD.

hydrochloride specifically targets vascular endothelial growth factors and related signaling factors, impeding their overexpression and promoting tumor vascular normalization, thereby repressing tumor cell proliferation and controlling disease progression[21]. This effect has been demonstrated in various tumor types, including CRC[22-26].

Sintilimab belongs to the recombinant human immunoglobulin G4-type anti-PD-1 and monoclonal antibody. Upon successful binding to PD-1, it effectively obstructs the interaction established between PD-1 and PD-L2, thereby alleviating the immunosuppressive impact. This action leads to the activation of T cells, intensifying their cytotoxicity against neoplastic cells, and ultimately inducing robust immune responses[27]. For MSS CRC patients, sintilimab is usually combined with other treatment modalities, such as chemotherapy drugs. Through the action of immune checkpoint inhibitors, sintilimab can heighten the activation level of immune cells against tumor cells and strengthen the ability of the immune system to attack tumors. In combination therapy, sintilimab can assist other treatment approaches, improve treatment efficacy, and prolong patient survival[28].

Based on this, we delved into the role of the combination of these two drugs in the clinical treatment of MSS CRC. The outcomes unraveled that the observation group exhibited better short-term and long-term efficacy, which may be attributed to the combined use of the two drugs, which not only exerted anti-tumor effects but also modulated the patients' immune system, strengthening the immunity-mediated killing effect on tumor cells and achieving better treatment outcomes. Previous works have also confirmed that the immune microenvironment functions significantly in

Table 5 Comparison of life quality

Indicators	Time	Observation group, *n* = 46	Control group, *n* = 46	*t*	*P* value
Functional domains	Before treatment	35.12 ± 4.06	35.40 ± 4.57	0.311	0.757
	After treatment	42.10 ± 6.06[1]	39.11 ± 5.74[1]	2.430	0.017
Symptom domains	Before treatment	17.52 ± 3.24	17.06 ± 3.00	0.707	0.482
	After treatment	10.42 ± 1.57[1]	14.20 ± 2.17[1]	9.572	0.000
General health status/quality of life domains	Before treatment	7.52 ± 0.85	7.23 ± 0.89	1.598	0.114
	After treatment	11.54 ± 1.47[1]	9.24 ± 1.03[1]	8.691	0.000
Individual item measurements	Before treatment	17.41 ± 2.09	17.26 ± 2.47	0.314	0.754
	After treatment	13.02 ± 1.22[1]	15.05 ± 1.54[1]	7.008	0.000

[1]Denotes a comparison with the pre-treatment values. Data are mean scores ± SD.

Table 6 Comparison of the incidence of adverse events between the two groups during the treatment period

Indicators	Observation group, *n* = 46	Control group, *n* = 46	χ^2	*P* value
Fever	1 (2.317)	1 (2.17)		
Fatigue	2 (4.35)	1 (2.17)		
Dizziness/headache	2 (4.35)	2 (4.35)		
Decreased appetite	2 (4.35)	1 (2.17)		
Diarrhea	2 (4.35)	1 (2.17)		
Total incidence	9 (19.57)	7 (15.22)	0.302	0.582

Data are *n* (%).

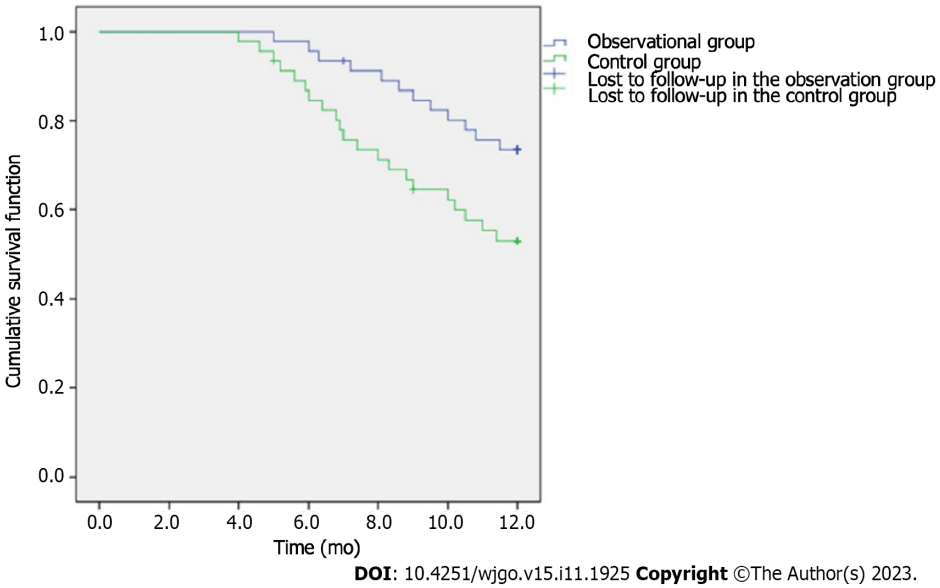

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Figure 1 Survival curves of 1-year follow-up in both groups.

the emergence and progression of malignancies. Moreover, the modulation of the tumor microenvironment is regarded as a new strategy for anti-tumor treatment. These findings are consistent with the results of this study[29].

CEA is produced by organs such as the intestines, liver, and pancreas and is commonly found in cancer tissue mucins and embryonic tissues. It is highly expressed in tumors, including CRC, gastric cancer, breast cancer, *etc*. CA199 is a glycoprotein complex with a high relative molecular weight, generated by epithelial cells in the pancreas, stomach, colon,

and other organs. It is usually present in the serum as a mucin and undergoes hepatic metabolism. After the occurrence of digestive tract malignancies such as rectal cancer and gastric cancer, CA199 shows a high expression. CA125 is a glycoprotein produced by tumor cells and presents a high profile in frequently encountered malignant tumors like gastric cancer and colon cancer[30,31].

The aforementioned markers are commonly used malignant tumor markers in clinical practice and are often utilized for assessing disease status and clinical treatment efficacy. Through the exploration conducted within this study, a notable revelation emerged that the serum concentrations of CEA, CA199, and CA125 were robustly reduced within the observation group subsequent to the applied treatment. This finding serves as evidence that the combination treatment protocol administered to individuals with MSS CRC can effectively curb the levels of CEA, CA199, and CA125. This may be due to the remarkable inhibitory impact of anlotinib hydrochloride on tumor microangiogenesis, leading to the disappearance of tumor microvessels. Furthermore, the activation of T cells by sintilimab triggers immune responses and kills tumor cells. The combination of these two treatments synergistically exerts anti-tumor effects through multiple pathways, hence dampening CEA, CA199, and CA125 profiles.

Following the intervention, the observation group exhibited remarkable enhancements in T lymphocyte subsets, surpassing not only their own pretreatment levels but also outperforming the post-treatment levels of the control group. This observation confirmed that combining sintilimab and anlotinib hydrochloride in MSS CRC treatment can regulate immune function. T cells are key cells in the immune response process, with CD4+ cells as inducer/helper T cells that exert a critical function in the modulation of immune responses, and CD8+ cells as cytotoxic/suppressor T cells that exhibit cytotoxicity and belong to an important type of cytotoxic effector cells[32]. The higher improvement in immune function monitored in the observation group may be attributed to the activation of T cell activity mediated by the addition of sintilimab.

During this process, it can target and bind to PD-1 on the surface of T cells and exert a PD-1/PD-L1 blocking effect, thereby promoting the reconstruction of tumor surveillance mechanisms and modulating the levels of T lymphocyte subsets CD4+, CD8+, and CD4+/CD8+. Liang and Wei[33] have also substantiated in clinical practice that sintilimab can regulate the immune function of malignant tumor patients, leading to better clinical treatment outcomes, which is aligned with the findings of this research.

Furthermore, the study also evaluated the quality of life before and after treatment in both groups and discovered that the scores for various dimensions of quality of life were better in the observation group as opposed to the control group subsequent to treatment. The analysis suggests that the better control of tumor cell proliferation and improvement in the immune system in the observation group after the combination therapy may be closely correlated with the observed improvement in life quality.

CONCLUSION

In summary, the combination of sintilimab and anlotinib hydrochloride in the treatment of MSS CRC patients can decrease CEA, CA199, and CA125 levels, regulate the immune system, improve prognosis, and demonstrate good clinical efficacy, which is worthy of attention by clinicians. Nevertheless, this study still has certain limitations. First, to ensure the smooth implementation of the study, there may be some bias in the selection of sample size. Second, this study only observed the therapeutic effects in MSS CRC patients, and it is still unclear whether there are differences in the efficacy of sintilimab combined with anlotinib hydrochloride between MSS CRC and non-MSS CRC patients. This could be one of the directions for future research by the research team.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is one of the most common types of cancer worldwide, accounting for a significant number of cancer-related deaths. Microsatellite stable (MSS) CRC is a subtype of CRC characterized by a stable genomic pattern. Traditional chemotherapy regimens have shown limited efficacy in treating MSS CRC, highlighting the need for novel therapeutic approaches. Immunotherapy, particularly immune checkpoint inhibitors, has emerged as a promising treatment strategy for various cancers, including MSS CRC.

Research motivation

Despite the substantial success of immune checkpoint inhibitors in the treatment of microsatellite instability-high CRC, their efficacy in MSS CRC remains uncertain. Additionally, the exploitation of combination therapies has emerged as a potential strategy to enhance treatment outcomes. Thus, exploring the combination of sintilimab (an anti-PD-1 monoclonal antibody) and anlotinib hydrochloride (a tyrosine kinase inhibitor) in the clinical treatment of MSS CRC could provide new insights and potential benefits.

Research objectives

The primary objective of this study was to evaluate the clinical efficacy and safety of sintilimab combined with anlotinib hydrochloride in the treatment of MSS CRC. Specifically, the study aimed to assess the safety profile, serum markers, and quality of life in MSS CRC patients receiving this combination therapy.

Research methods

In a study conducted from 2019 to 2022, 92 patients diagnosed with CRC were divided into an observation group and a control group. The observation group received additional treatment with sintilimab on top of the treatment given to the control group, which received anlotinib hydrochloride. Treatment was administered in cycles of 3 wk, and after two consecutive cycles, the efficacy was evaluated.

Research results

The observation group showed significantly better short-term efficacy compared to the control group (76.09% *vs* 50.00%, $P < 0.05$). The observation group also exhibited significant decreases in serum markers after treatment, which were lower than both the pretreatment levels and the post-treatment levels in the control group ($P < 0.05$). The T cell subset levels in the observation group significantly improved after treatment and surpassed both the pretreatment levels and the post-treatment levels in the control group ($P < 0.05$). Additionally, the observation group demonstrated significant improvements in various dimensions of quality of life, surpassing both the pretreatment levels and the post-treatment levels in the control group ($P < 0.05$). During the 1-year follow-up period, 1 patient in the observation group and 2 patients in the control group were lost to follow-up. In the observation group, 12 patients died, resulting in a survival rate of 73.33% (33/45), while in the control group, 21 patients died, resulting in a survival rate of 52.27% (23/44). Kaplan-Meier survival analysis showed a significant difference in survival rates between the two groups (log-rank = 4.710, $P = 0.030$).

Research conclusions

The combination of sintilimab and anlotinib hydrochloride demonstrated significant efficacy in the treatment of CRC patients, improving immunity and prognosis.

Research perspectives

While this study provided valuable insights into the efficacy and safety of sintilimab combined with anlotinib hydrochloride in MSS CRC, further research is warranted. Future studies could focus on exploring the underlying mechanisms of the observed therapeutic effects, defining predictive biomarkers for treatment response, and optimizing the treatment regimen. Additionally, investigating the potential synergy between immunotherapy and other targeted therapies may enhance treatment outcomes in MSS CRC and advance precision medicine approaches.

FOOTNOTES

Author contributions: Feng R and Wu H designed the study; Cheng DX, Chen XC, and Yang L performed the experiments; Feng R, Cheng DX, and Chen CX analyzed the data; Feng R wrote the manuscript; Wu H reviewed and revised the manuscript; All authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by Ethics Committee of Zhejiang Provincial People's Hospital.

Informed consent statement: The data used in this study were not involved in the patients' privacy information, so the informed consent was waived by the Ethics Committee of Zhejiang Provincial People's Hospital. All data obtained, recorded, and managed was only used for this study, without any harm to the patients.

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REFERENCES

1 **Patel SG**, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol* 2022; **7**: 262-274 [PMID: 35090605 DOI: 10.1016/S2468-1253(21)00426-X]

2 **Ciardiello F**, Ciardiello D, Martini G, Napolitano S, Tabernero J, Cervantes A. Clinical management of metastatic colorectal cancer in the era of precision medicine. *CA Cancer J Clin* 2022; **72**: 372-401 [PMID: 35472088 DOI: 10.3322/caac.21728]

3 **Zhao H**, Ming T, Tang S, Ren S, Yang H, Liu M, Tao Q, Xu H. Wnt signaling in colorectal cancer: pathogenic role and therapeutic target. *Mol Cancer* 2022; **21**: 144 [PMID: 35836256 DOI: 10.1186/s12943-022-01616-7]

4 **Donátová K**, Nováková E, Šupolíková M. Immunotherapy for cancer treatment. *Klin Onkol* 2022; **35**: 284-289 [PMID: 35989085 DOI: 10.48095/ccko2022284]

5 **Chen Y**, Bai B, Ying K, Pan H, Xie B. Anti-PD-1 combined with targeted therapy: Theory and practice in gastric and colorectal cancer. *Biochim Biophys Acta Rev Cancer* 2022; **1877**: 188775 [PMID: 35934154 DOI: 10.1016/j.bbcan.2022.188775]

6 **Tang YL**, Li DD, Duan JY, Sheng LM, Wang X. Resistance to targeted therapy in metastatic colorectal cancer: Current status and new developments. *World J Gastroenterol* 2023; **29**: 926-948 [PMID: 36844139 DOI: 10.3748/wjg.v29.i6.926]

7 **Taieb J**, Svrcek M, Cohen R, Basile D, Tougeron D, Phelip JM. Deficient mismatch repair/microsatellite unstable colorectal cancer: Diagnosis, prognosis and treatment. *Eur J Cancer* 2022; **175**: 136-157 [PMID: 36115290 DOI: 10.1016/j.ejca.2022.07.020]

8 **Bai Z**, Zhou Y, Ye Z, Xiong J, Lan H, Wang F. Tumor-Infiltrating Lymphocytes in Colorectal Cancer: The Fundamental Indication and Application on Immunotherapy. *Front Immunol* 2021; **12**: 808964 [PMID: 35095898 DOI: 10.3389/fimmu.2021.808964]

9 **Ooki A**, Shinozaki E, Yamaguchi K. Immunotherapy in Colorectal Cancer: Current and Future Strategies. *J Anus Rectum Colon* 2021; **5**: 11-24 [PMID: 33537496 DOI: 10.23922/jarc.2020-064]

10 **Fan A**, Wang B, Wang X, Nie Y, Fan D, Zhao X, Lu Y. Immunotherapy in colorectal cancer: current achievements and future perspective. *Int J Biol Sci* 2021; **17**: 3837-3849 [PMID: 34671202 DOI: 10.7150/ijbs.64077]

11 **Wang YM**, Meng Y, Shi XN, Fan SR, Song M. [Analysis of clinical efficacy, safety and prognosis of anlotinib hydrochloride in the treatment of advanced primary liver cancer]. *Zhonghua Gan Zang Bing Za Zhi* 2020; **28**: 619-624 [PMID: 32791800 DOI: 10.3760/cma.j.cn501113-20191020-00385]

12 **Ren Z**, Xu J, Bai Y, Xu A, Cang S, Du C, Li Q, Lu Y, Chen Y, Guo Y, Chen Z, Liu B, Jia W, Wu J, Wang J, Shao G, Zhang B, Shan Y, Meng Z, Gu S, Yang W, Liu C, Shi X, Gao Z, Yin T, Cui J, Huang M, Xing B, Mao Y, Teng G, Qin Y, Xia F, Yin G, Yang Y, Chen M, Wang Y, Zhou H, Fan J; ORIENT-32 study group. Sintilimab plus a bevacizumab biosimilar (IBI305) *vs* sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. *Lancet Oncol* 2021; **22**: 977-990 [PMID: 34143971 DOI: 10.1016/S1470-2045(21)00252-7]

13 **Yu C**, Jiang L, Yang D, Dong X, Yu R, Yu H. Anlotinib Hydrochloride and PD-1 Blockade as a Salvage Second-Line Treatment in Patients with Progress of Local Advanced Non-Small Cell Lung Cancer in Half a Year After Standard Treatment. *Onco Targets Ther* 2022; **15**: 1221-1228 [PMID: 36262804 DOI: 10.2147/OTT.S380615]

14 **Therasse P**, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205-216 [PMID: 10655437 DOI: 10.1093/jnci/92.3.205]

15 **Huang CC**, Lien HH, Sung YC, Liu HT, Chie WC. Quality of life of patients with gastric cancer in Taiwan: validation and clinical application of the Taiwan Chinese version of the EORTC QLQ-C30 and EORTC QLQ-STO22. *Psychooncology* 2007; **16**: 945-949 [PMID: 17279609 DOI: 10.1002/pon.1158]

16 **Grimes N**, Tyson M, Hannan C, Mulholland C. A Systematic Review of the Prognostic Role of Hematologic Scoring Systems in Patients With Renal Cell Carcinoma Undergoing Nephrectomy With Curative Intent. *Clin Genitourin Cancer* 2016; **14**: 271-276 [PMID: 26949171 DOI: 10.1016/j.clgc.2016.01.006]

17 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

18 **Parisi A**, Porzio G, Cannita K, Venditti O, Avallone A, Filippi R, Salvatore L, Tortora G, Ribelli M, Nigro O, Gelsomino F, Spallanzani A, Zurlo V, Leo S, Dell'Aquila E, Claudia F, Lombardi P, Keränen SR, Aimar G, Depetris I, Giampieri R, Morelli C, De Tursi M, Tinari N, Di Pietro FR, De Galitiis F, Zanaletti N, Troiani T, Vitale P, Garajova I, Ghidini M, Spinelli GP, Zoratto F, Roberto M, Ierino D, Petrillo A, D'Orazio C, Ficorella C, Cortellini A. Clinicians' Attitude to Doublet Plus Anti-EGFR Versus Triplet Plus Bevacizumab as First-line Treatment in Left-Sided RAS and BRAF Wild-Type Metastatic Colorectal Cancer Patients: A Multicenter, "Real-Life", Case-Control Study. *Clin Colorectal Cancer* 2021; **20**: 318-325 [PMID: 34380594 DOI: 10.1016/j.clcc.2021.07.003]

19 **Wang J**, Wu DX, Meng L, Ji G. Anlotinib combined with SOX regimen (S1 (tegafur, gimeracil and oteracil porassium capsules) + oxaliplatin) in treating stage IV gastric cancer: study protocol for a single-armed and single-centred clinical trial. *BMJ Open* 2020; **10**: e034685 [PMID: 32499264 DOI: 10.1136/bmjopen-2019-034685]

20 **Lugano R**, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. *Cell Mol Life Sci* 2020; **77**: 1745-1770 [PMID: 31690961 DOI: 10.1007/s00018-019-03351-7]

21 **Syed YY**. Anlotinib: First Global Approval. *Drugs* 2018; **78**: 1057-1062 [PMID: 29943374 DOI: 10.1007/s40265-018-0939-x]

22 **Wang J**, Li K. [Research progress of anti-angiogenic drugs in the treatment of small cell lung cancer]. *Zhonghua Zhong Liu Za Zhi* 2020; **42**: 624-628 [PMID: 32867452 DOI: 10.3760/cma.j.cn112152-20200217-00097]

23 **Luo Q**, Zhang S, Zhang D, Feng R, Li N, Chen W, Chen X, Yang S. Effects and Mechanisms of Anlotinib and Dihydroartemisinin Combination Therapy in Ameliorating Malignant Biological Behavior of Gastric Cancer Cells. *Curr Pharm Biotechnol* 2021; **22**: 523-533 [PMID: 32576126 DOI: 10.2174/1389201021666200623132803]

24 **Wang G**, Sun M, Jiang Y, Zhang T, Sun W, Wang H, Yin F, Wang Z, Sang W, Xu J, Mao M, Zuo D, Zhou Z, Wang C, Fu Z, Duan Z, Hua Y, Cai Z. Anlotinib, a novel small molecular tyrosine kinase inhibitor, suppresses growth and metastasis *via* dual blockade of VEGFR2 and MET in osteosarcoma. *Int J Cancer* 2019; **145**: 979-993 [PMID: 30719715 DOI: 10.1002/ijc.32180]

25 **Yang Q**, Ni L, Imani S, Xiang Z, Hai R, Ding R, Fu S, Wu JB, Wen Q. Anlotinib Suppresses Colorectal Cancer Proliferation and Angiogenesis *via* Inhibition of AKT/ERK Signaling Cascade. *Cancer Manag Res* 2020; **12**: 4937-4948 [PMID: 32606981 DOI: 10.2147/CMAR.S252181]

26 **Chi Y**, Shu Y, Ba Y, Bai Y, Qin B, Wang X, Xiong J, Xu N, Zhang H, Zhou J, Xu J, Cheng Y, Feng J, Hu C, Chen Y, Chen Z, Wang J, Dang C, Wan Y, Tang Y, Wang D, Liu J, Wu M, Deng Y, Li X, Li Y, Dong J, Jiang D, Li G, Wu Q, Li J, Qi Y, Sun Y, Cai J. Anlotinib Monotherapy for Refractory Metastatic Colorectal Cancer: A Double-Blinded, Placebo-Controlled, Randomized Phase III Trial (ALTER0703). *Oncologist* 2021; **26**: e1693-e1703 [PMID: 34105207 DOI: 10.1002/onco.13857]

27 **Guo L**, Qu W, Wei Y, Liang L, Tang Y, Chen C, Ke X. Sintilimab plus chemotherapy achieved symptom relief in stage IV lung squamous cell carcinoma with superior vena cava syndrome: a case report. *Ann Palliat Med* 2022; **11**: 401-406 [PMID: 35144431 DOI: 10.21037/apm-21-3674]

28 **Yi M**, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. *Mol Cancer* 2022; **21**: 28 [PMID: 35062949 DOI: 10.1186/s12943-021-01489-2]

29 **Cheng YQ**, Wang SB, Liu JH, Jin L, Liu Y, Li CY, Su YR, Liu YR, Sang X, Wan Q, Liu C, Yang L, Wang ZC. Modifying the tumour microenvironment and reverting tumour cells: New strategies for treating malignant tumours. *Cell Prolif* 2020; **53**: e12865 [PMID: 32588948 DOI: 10.1111/cpr.12865]

30 **Lertkhachonsuk AA**, Buranawongtrakoon S, Lekskul N, Rermluk N, Wee-Stekly WW, Charakorn C. Serum CA19-9, CA-125 and CEA as tumor markers for mucinous ovarian tumors. *J Obstet Gynaecol Res* 2020; **46**: 2287-2291 [PMID: 32830422 DOI: 10.1111/jog.14427]

31 **Liu T**, Li X, Liu D, Liu S, Dong M. Increased serum CA125 II, but not CEA, CA19-9, AFP or CA72-4 in colon cancer compared to rectal cancer. *Br J Biomed Sci* 2021; **78**: 218-220 [PMID: 33393429 DOI: 10.1080/09674845.2020.1868685]

32 **van der Leun AM**, Thommen DS, Schumacher TN. CD8(+) T cell states in human cancer: insights from single-cell analysis. *Nat Rev Cancer* 2020; **20**: 218-232 [PMID: 32024970 DOI: 10.1038/s41568-019-0235-4]

33 **Liang X**, Wei Z. Effect of Sintilimab combined with Chemotherapy on Tumor Markers and Immune Function of advanced non-small cell lung cancer. *Pak J Med Sci* 2021; **37**: 1063-1068 [PMID: 34290784 DOI: 10.12669/pjms.37.4.3820]

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