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Effects of mFOLFOX6 regimen combined with carrelizumab on immune function and prognosis in patients with microsatellite instability colorectal cancer

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ABSTRACT

This study aimed to investigate the effect of the mFOLFOX6 regimen combined with SHR-1210 on immune function and prognosis in patients with microsatellite instability CRC. For this purpose, 60 patients with microsatellite instability CRC in our hospital from January 2019 to October 2020 were randomly divided into control and observation groups. The control group was treated with the mFOLFOX6 regimen, and the observation group was treated with s SHR-1210. After continuous treatment for 3 months, the clinical effects of the two groups were compared; CD4+, CD8+, CD4+/CD8+; IgA, IgG, IgM; Incidence of adverse reactions and PFS. The results showed that compared with the control group (30.00%), the total clinical effective rate in the observation group (53.33%) was significantly higher ($P < 0.05$). After treatment, CD4+, CD4+/ CD8+ decreased significantly and CD8+ increased significantly, and the change range of the observation group was significantly less than the control group ($P < 0.05$. The levels of IgA, IgG and IgM in the two groups decreased significantly after treatment, and the decrease in the observation group was significantly less than the control group ($P < 0.05$). There was no significant difference in the incidence of abnormal liver function, bleeding, proteinuria, neurotoxicity, gastrointestinal reaction, leucopenia and hypertension between the two groups ($P > 0.05$). PFS in the observation group was significantly prolonged after treatment ($P < 0.05$). In general, **the** mFOLFOX6 regimen combined with SHR-1210 is effective in the treatment of microsatellite instability CRC. It can not only improve the immune function, but also not increase adverse reactions, prolong the survival time, and has a high clinical reference value.

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Introduction

Colorectal cancer (CRC) is a common malignant gastrointestinal tumor with high morbidity and mortality (1). With the development of society and the change of lifestyle, the incidence of CRC keeps increasing and gradually tends to be younger, posing a great threat to human health and living standards (2, 3). A microsatellite is an important nucleotide sequence of some small fragments in the genome (4). The base mismatch may occur in the replication process of Deoxyribonucleic acid (DNA), which may lead to gene mutation after accumulation and eventually cause cell canceration (5). Relevant studies have shown that microsatellite instability (MSI) is an important factor affecting the progression of CRC disease and can lead to a poor prognosis (6). Therefore, how to treat microsatellite unstable CRC has become one of the key projects of clinical research. Modifying calcium folinate and fluorouracil combined with oxaliplatin are currently used to treat CRC patients with chemotherapy. MFOLFOX6 (mFOLFOX6) is a commonly used chemotherapy regimen in the clinic, although it has a certain control effect on the disease. However, its toxic side effects are strong and the clinical prognosis is poor (7). Programmed Cell Death Protein-1 (PD-1) inhibitor camrelizumab is programmed cell death Protein-1 (PD-1) Programmed death ligand-1 (pd-l1) pathway can be blocked by binding pd-1 to restore the body's anti-tumor immunity and thus form the basis of immunotherapy (8-10). Some scholars have found that SHR-1210 combined with chemotherapy can effectively improve the quality of life of cancer patients (11, 12), but there are few studies on the

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effect of mFOLFOX6 combined with SHR-1210 on microsatellite unstable CRC patients, which is worthy of further study. Therefore, this study mainly explored the effects of the mFOLFOX6 regimen combined with SHR-1210 on immune function and prognosis of patients with microsatellite unstable CRC, aiming to provide more reference ideas for clinical treatment of microsatellite unstable CRC.

Materials and methods

General Information

A total of 60 patients with MICROsatellite unstable CRC admitted to our hospital from January 2019 to October 2020 were selected as the research objects, and divided into control group (n = 30) and observation group (n = 30) according to the random number table method. The control group was treated with the mFOLFOX6 regimen, and the observation group was treated with SHR-1210 based on it. This study was approved by the hospital Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: All patients were diagnosed with microsatellite unstable CRC by barium X-ray, computed tomography (CT), magnetic resonance imaging (MRI) and immunohistochemical examination; Patients receiving related treatment for the first time; Patients with normal heart, liver and kidney function; patients who could follow up for 12 months; Informed consent was signed by patients or their families.

Exclusion criteria: Patients with the allergic constitution or drug allergy to the study; Patients with a history of immunosuppressant use or complicated immune system diseases; Patients with other malignant tumors; Patients who quit or died; Pregnant or lactating women.

Treatment methods

The control group was treated with mFOLFOX6 regimen: oxaliplatin (Zhejiang Haizhen Pharmaceutical Co., LTD., National Drug Approval LETTER H20093487) for 3 hours on day 1; Intravenous injection of 5-fluorouracil (Nantong General Factory, National drug approval word H22023469), 400mg/m2 on the first day, and 2400 mg/m2 on the following 46h; On the first and second days, two hours before the administration of 5-fluorouracil, 400mg/m2 calcium folate was given intravenously (jiangsu hengrui pharmaceutical co., LTD., national drug approval letter H20000584). Treatment was given once every 2 weeks.

The observation group was treated with SR-1210 based on the control group: intravenous infusion of 200mg SR-1210 (Suzhou Shengdia Biomedical Co., LTD., S20190027), once every 3 weeks.

After 3 months of continuous treatment, the therapeutic effect of the two groups was evaluated.

Clinical efficacy

Response evaluation criteria in solid tumors (RECIST) criteria (13), complete remission (CR) rate, which refers to the disappearance of lesions for at least 1 month, Partial remission (PR) rate refers to a reduction of at least 50% in focal area over at least one month. Stable disease (SD) refers to a decrease of less than 50% or an increase of 25% or less in the lesion area for at least one month. Progressive disease (PD) refers to an increase of more than 25% in the lesion area or the emergence of new lesions. The total clinical response rate was (CR+PR)/N ×100%.

Cellular immune function

5mL of morning fasting elbow venous blood was extracted from patients 1 day before treatment and 3 months after treatment, respectively, and placed in EP tube. After standing at room temperature for 1 h, serum was separated by centrifugation method and stored at -25℃ for testing. The levels of CD4+ and CD8+ of cellular immune indexes were detected by flow cytometry (FACS Canto II), and CD4+/CD8+ was calculated.

Humoral immune function

Serum samples were collected from the children, and the levels of Immunoglobulin A (IgA), Immunoglobulin G (IgG) and Immunoglobulin M (IgM) in the two groups were detected by rate scattering turbidimetry. The kits were provided by Shanghai Lanji Biotechnology Co., LTD.

Incidence of adverse reactions and Progress free survival (PFS)

Abnormal liver function, bleeding, proteinuria, neurotoxicity, gastrointestinal reactions, leucopenia, hypertension and other adverse reactions were

observed in both groups, and their severity was assessed. Grade I: mild signs and symptoms, which were improved immediately after drug withdrawal; Grade II: cause temporary damage, can improve after intervention or treatment, recovery quickly, without hospitalization; Grade III: prolonged hospitalization or hospitalization for treatment; Grade IV: permanent damage to tissues and organs (14). PFS in both groups (beginning with randomization and ending with first cancer progression or death) was recorded during a 12-month follow-up.

Statistical analysis

SPSS 18.0 was used for statistical analysis. The measurement data were expressed as mean ± standard deviation (± S) and tested by T. Enumeration data were expressed by example (n) or percentage (%) and tested by χ2. P<0.05 indicated a statistically significant difference.

Results and discussion

Comparison of general data between the two groups

There were no statistically significant differences in gender, age, tumor location and differentiation degree between the two groups (P>0.05), indicating comparability, as shown in Table 1.

Table 1. Comparison of general information of the two groups of patients

General information		Control group (n=30)	Observation group (n=30)	t/χ^2	P
Gender [N (%)]	Male	16 (53.33)	17 (56.67)	0.023	0.887
	Female	14 (46.67)	13 (43.33)		
Average age (years)		61.24±6.50	61.63±6.32	0.372	0.708
Tumor location [N (%)]	Left half colon	7 (23.33)	8 (26.67)	0.473	0.492
	Right colon	16 (53.33)	17 (56.67)		
	Rectum	7 (23.33)	5 (16.67)		
Degree of differentiation [N (%)]	High differentiation	7 (23.33)	8 (26.67)	0.454	0.501
	moderately differentiated	16 (53.33)	16 (53.33)		
	undifferentiated	7 (23.33)	6 (20.00)		

Comparison of clinical efficacy between the two groups

The total clinical effective rate of the observation group was significantly higher than that of the control group, with statistical significance (P<0.05), as shown in Table 2.

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Clinical curative effect	Control group (n=30)	Observation group (n=30)	χ^2	P
CR	1 (3.33)	2 (6.67)	-	-
PR	8 (20.00)	14（46.67）	-	-
SD	15 (53.33)	12（40.00）	-	-
PD	6 (23.33)	2（6.67）	-	-
Total	9 (30.00)	16（53.33）	5.689	0.027

Comparison of cellular immune function between the two groups before and after treatment

There were no significant differences in CD4+, CD8+ and CD4+/CD8+ between the two groups before treatment (P>0.05). After treatment, CD4+ and CD4+/CD8+ in the two groups were significantly decreased, while CD8+ was significantly increased. The range of change in the observation group was significantly smaller than that in the control group, with statistical significance (P<0.05), as shown in Table 3.

Table 3. Comparison of cellular immune function between the two groups before and after treatment ($\bar{x}$±s)

Index		Control group (n=30)	Observation group (n=30)
CD4+ (%)	Before the treatment	35.67±7.11	35.89±7.18
	After the treatment	31.24±5.78*	33.89±5.85*#
CD8+ (%)	Before the treatment	25.02±3.46	25.08±3.43
	After the treatment	28.57±5.74*	27.44±5.59*#
CD4+/CD8+	Before the treatment	1.62±0.22	1.63±0.24
	After the treatment	1.03±0.19*	1.34±0.16*#

Note: Compared with before treatment, *P<0.05, compared with control group, #P<0.05.

Comparison of humoral immune function between the two groups before and after treatment

Before treatment, there was no significant difference in IgA, IgG and IgM levels between the two groups (P>0.05). After treatment, IgA, IgG and IgM levels in the two groups decreased significantly. The decrease range in the observation group was significantly smaller than that in the control group, and the difference was statistically significant (P<0.05), as shown in Table 4.

Table 4. Comparison of humoral immune function between the two groups before and after treatment ($\bar{x}$±s, g/L)

Index		Control group (n=30)	Observation group (n=30)
IgA	Before the treatment	1.93±0.33	1.98±0.35
	After the treatment	1.14±0.34*	1.55±0.35*#
IgG	Before the treatment	10.48±1.20	10.43±1.17
	After the treatment	8.05±1.39*	9.01±1.29*#
IgM	Before the treatment	1.69±0.20	1.78±0.23
	After the treatment	1.16±0.13*	1.42±0.09*#

Note: Compared with before treatment, *P<0.05, compared with control group, #P<0.05.

Comparison of adverse reactions and PFS between the two group

There was no significant difference in the incidence of abnormal liver function, bleeding, proteinuria, neurotoxicity, gastrointestinal reaction, leucopenia and hypertension between the two groups (P>0.05), and PFS in the observation group was significantly longer than that in the control group. The difference was statistically significant (P<0.05), as shown in Table 5.

Table 5. Comparison of adverse reactions and PFS between the two groups

Project		Control group (n=30)	Observation group (n=30)	χ^2	P
Hepatic dysfunction	I ~ II	8 (26.67)	9 (30.00)		
	III ~ IV	0 (0.00)	1 (3.33)	0.344	0.569
Total		8 (26.67)	10 (33.33)		
Bleeding	I ~II	0 (0.00)	1 (3.33)		
	III ~ IV	0 (0.00)	0 (0.00)	1.020	0.312
Total		0 (0.00)	1 (3.33)		
Proteinuria	I ~II	2 (6.67)	3 (10.00)		
	III ~ IV	0 (0.00)	0 (0.00)	0.221	0.639
Total		2 (6.67)	3 (10.00)		
Neurotoxicity	I ~II	1 (3.33)	2 (6.67)		
	III ~ IV	0 (0.00)	0 (0.00)	0.354	0.552
Total		1 (3.33)	2 (6.67)		
Gastrointestinal reaction	I ~II	14 (46.67)	15 (50.00)		
	III ~ IV	2 (6.67)	2 (6.67)	0.072	0.790
Total		16 (53.33)	17 (56.67)		
Leucopenia	I ~II	3 (10.00)	4 (13.33)		
	III ~ IV	1 (3.33)	2 (6.67)	0.485	0.486
Total		4 (13.33)	6 (20.00)		
Hypertension	I ~II	2 (6.67)	3 (10.00)		
	III ~ IV	0 (0.00)	1 (3.33)	0.746	0.388
Total		2 (6.67)	4 (13.33)		
PFS (Month)		6.28±1.26	8.19±1.47	7.128	0.000

CRC is one of the three major malignant tumors in the world, with high morbidity and mortality and an increasing trend, posing a serious threat to human health and life safety (15, 16). Early detection, diagnosis and treatment can significantly improve the quality of life of CRC patients (17). However, THE growth rate of CRC tumor is relatively slow, and most patients have no obvious symptoms in the early stage, with strong conceal ability. Most patients have reached the middle and late stage of tumor when diagnosed and may have MSI, which increases the difficulty of clinical treatment (18, 19). MFOLFOX6 regimen is one of the main clinical treatment regimens for metastatic CRC at present, but it has many adverse reactions, which is not conducive to the prognosis of patients (20). In recent years, immune checkpoint inhibitors (ICIs) have made breakthrough progress in clinical practice. Due to their good tolerance and growth advantages, they have been widely used in the clinical treatment of tumor diseases, effectively prolonging the survival period of patients. Shr-1210 is a common ICIs (21). However, few studies have explored the effect of mFOLFOX6 combined with mFOLFOX6 on immune function and prognosis of patients with microsatellite unstable CRC.

Liu et al. (22) explored the therapeutic effect of SR-1210 combined with sorafenib on patients with advanced liver cancer, and the results showed that the total effective rate of SR-1210 combined with sorafenib was higher than that of sorafenib alone. In this study, the total clinical response rate of the observation group was significantly higher than that of the control group, which was basically consistent with the results of Liu's study, indicating that the mFOLFOX6 regimen combined with SHR-1210 can effectively treat microsatellite unstable CRC. 5-fluorouracil in mFOLFOX6 regimen is an antitumor drug commonly used in clinical practice and has achieved good efficacy in the treatment of malignant tumors. Oxaliplatin is a platinum agent, which can generate complex through contacting DNA, hinder the replication and transcription of DNA double strands, and then promote cell apoptosis, and play a synergistic anti-tumor effect with 5-fluorouracil. Calcium folate can increase the anti-tumor effect of 5-fluorouracil (23, 24). As a monoclonal antibody against Immunoglobulin G4 (IgG4), SHR-1210 blocks the binding of PD-1/PD-L1 by binding PD-1, cuts off the immune escape pathway of tumor cells, reactivates the immune response, and gradually restores the function of immune monitoring. It can improve the

recognition and killing function of T lymphocytes to tumor cells. Finally, its anti-tumor effect is exerted (25, 26). The combination of mFOLFOX6 and SHR-1210 has a synergistic effect and exerts anti-tumor effects from different mechanisms respectively.

Body immunity can be divided into cellular immunity and humoral immunity. Cellular immunity mainly comes from T lymphocytes, and CD3+ is expressed in mature T cell subsets, which can improve the rate of antigen recognition. The higher the CD3+ level is, the higher the recognition ability is, and the better the immune function is. CD4+ can play a supportive role in the body's immunity, while CD8+ can inhibit the metastasis, diffusion and growth of tumor cells. CD4+/CD8+ can reflect the immune status of the body, and keep in a dynamic equilibrium state in the middle of the normal body, once decreased, it indicates the decrease of cellular immune function (27). Immunoglobulin is one of the commonly used detection methods for the humoral immune function of the body. When an abnormal decrease of IgA, IgG and IgM levels of immunoglobulin is found, humoral immune deficiency of the body can be determined (28). The results of this study showed that CD4+, CD4+/CD8+, IgA, IgG and IgM decreased and CD8+ increased in the two groups after treatment, while the change range was small in the observation group, indicating that mFOLFOX6 regimen combined with SHR-1210 can reduce the influence on immune function of microsatellite unstable CRC patients to a certain extent. Chemotherapeutic drugs can play a dual role: on the one hand, they can kill tumor cells, reduce tumor load, and then remove the immune suppression of the body; on the other hand, they can produce a certain non-selective killing effect, which affects the active lymphoid system, and then reduce the immune function of the body. Shr-1210 plays an anti-tumor role by enhancing the immune function of the body through specific targeted binding with PD-1 to block the binding of PD-L1 and programmed death ligand-2 (PD-L2) (29).

MSI can cause poor prognosis of CRC, and its mechanism may be as follows: Increased cyclin-oxyge-Nase 2 (COX-2) expression promotes the metastasis of cancer cells, reduces cell apoptosis and promotes the regeneration of cancer vessels; It promoted the release of CD8+ and had killing effect on cellular immunity; MSI is mainly caused by the deletion of the mismatch repair gene system (MMR), which leads to the deletion or restricted expression of a variety of genes, leading to the down-regulation of signaling pathways (30). Qin et al. (31) showed that SR-1210 had good anti-tumor activity and controllable toxicity. In this study, there was no significant difference in the incidence of adverse reactions such as abnormal liver function, bleeding and proteinuria between the two groups, which was consistent with the results of Qin study. Meanwhile, the length of PFS in the observation group was significantly longer than that in the control group, indicating that mFOLFOX6 combined with SHR-1210 could effectively improve the prognosis of patients with microsatellite unstable CRC. Sr-1210 can cause a variety of immune-related adverse reactions, involving liver, endocrine, skin and other systems. However, relevant studies have shown that its combination with chemotherapy can effectively reduce the risk of its occurrence, and the specific mechanism is not completely clear (32).

In conclusion, mFOLFOX6 combined with SHR-1210 can effectively improve the clinical efficacy and immune function of patients with microsatellite unstable CRC, with little impact on adverse reactions, and prolong the survival of patients, which is worthy of clinical reference.

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None.

Interest conflict

The authors declare no conflict of interest.

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