Clinical Observation of Regorafenib Combined with Immune Checkpoint Inhibitor for Advanced Colorectal Cancer of pMMR/MSS Type

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Abstract: *Objective:* To observe the clinical efficacy and safety of regorafenib combined with immune checkpoint inhibitors in the treatment of patients with advanced colorectal cancer of pMMR/MSS type. *Methods:* 42 patients with advanced colorectal cancer of pMMR/MSS type admitted to the Department of Oncology of our hospital from January 2022 to September 2023 were randomly divided into the observation group and the control group, 21 cases each. The observation group was treated with the addition of regorafenib combined with immune checkpoint inhibitors, while the control group was given regorafenib monotherapy, and the efficacy, adverse effects, and survival of patients in the two groups were observed. *Results:* the total remission rate of the control group was 23.81%, and the total remission rate of the observation group was 57.14%, and the difference between the two groups was statistically significant ($P < 0.05$); there were 14 cases of adverse reactions in the two groups, with an incidence rate of 33.33% (14/42); and the overall survival rate of the observation and control groups was 71.43% and 47.62%, respectively. The survival rate of the observation group was higher than that of the control group, but the difference was not statistically significant ($P > 0.05$). *Conclusion:* Regorafenib combined with anti-PD-1 monoclonal antibody can significantly improve the efficacy and prognosis of advanced colorectal cancer without increasing adverse effects.

Keywords: Regorafenib; Immune checkpoint inhibitor; Colorectal cancer; Effectiveness

1. Introduction

Colorectal cancer (CRC) is one of the malignant tumors with high morbidity and mortality worldwide. In recent years, with the change in lifestyle and the aging trend of the population, its incidence rate has also shown a rising trend year by year in China. Despite the continuous improvement of traditional treatments such as surgery, chemotherapy, radiotherapy, etc., the prognosis of patients with advanced colorectal cancer is still not optimistic, especially pMMR/MSS (Proficient Mismatch Repair/Microsatellite Stable) type patients, whose therapeutic effect is particularly poor due to the lack of effective therapeutic targets. Immune checkpoint inhibitors (ICIs), a major breakthrough in the field of tumor immunotherapy in recent years, activate the body's

own immune system to attack tumor cells by blocking their immune escape mechanism [1]. However, the limited efficacy of single use of ICIs in pMMR/MSS-type advanced colorectal cancer is mainly due to the lack of sufficient immunogenicity of this tumor type to trigger an effective immune response. Regorafenib is an oral multikinase inhibitor approved for the treatment of advanced colorectal cancer, which exerts antitumor effects by inhibiting a variety of kinases associated with tumor growth, angiogenesis, and the tumor microenvironment. Recent studies have found that regorafenib enhances the immunogenicity of tumor cells, making the tumor a target of the immune system [2]. Therefore, combining regorafenib with immune checkpoint inhibitors is expected to improve the therapeutic efficacy of pMMR/MSS-type advanced colorectal cancer. This study aims to investigate the clinical effect of regorafenib combined with immune checkpoint inhibitors in the treatment of pMMR/MSS-type advanced colorectal cancer and its possible mechanism of action, through which it is hoped to provide patients with pMMR/MSS-type advanced colorectal cancer with a more effective therapeutic strategy, to improve their quality of life and to prolong their survival.

2. Materials and methods

2.1. General information

From January 2020 to September 2023, 42 patients with advanced colorectal cancer of stage III-IV pMMR/MSS type admitted to the Department of Oncology of Affiliated Hospital of Hebei Engineering University treated with the combination therapy of regorafenib and immune checkpoint inhibitor were randomly divided into the observation group and the control group, each with 21 cases. The control group consisted of 16 male cases and 5 female cases, aged 21–76 years, with an average age of 59.12 ± 8.69 years, while the observation group had 14 male cases and 7 female cases, aged 28–79 years, with an average age of 60.12 ± 9.01 years. The general information of the two groups of patients is not statistically significant and the difference is comparable.

Inclusion criteria: (1) Pathohistologic diagnosis of pMMR/MSS type CRC; (2) Age $\geq$ 18 years; (3) ECOG score $\leq$ 2; (4) Assessable lesions; (5) No contraindications such as severe cardiovascular and cerebrovascular diseases and liver and kidney dysfunction; (6) No previous chemotherapy or targeted therapy.

Exclusion criteria: (1) Non-colorectal tumors, adenocarcinoma, high-grade intraepithelial neoplasia, and other organ metastases; (2) Coexisting autoimmune diseases, such as thyroiditis, SLE, rheumatoid arthritis, desiccation syndrome, ankylosing spondylitis, etc.; (3) Intolerant of intravenous infusion of drugs; (4) Allergic to regorafenib-natalizumab injection (anti-PD1 antibody) or atilizumab injection (anti-PD-1 antibody).

2.2. Methods

Patients in the control group were given regorafenib monotherapy with 100 mg/m^2, four times a day, in the 1st cycle, which was administered continuously until disease progression or intolerable toxicity response, but the specific tolerable response depended on the overall condition of the patient and tumor load. Patients in the observation group were treated with natalizumab in combination with regorafenib on top of the control group, and both drugs were administered by subcutaneous injection. All patients received a platinum-based chemotherapy regimen at a dose of 40 mg/m^2 for days 1–15, with a total number of chemotherapy cycles not exceeding four, and then continued to be given the next round of chemotherapy if the patients were able to tolerate it. All patients were followed up to observe the efficacy, adverse effects, and survival. The patients in both groups underwent corresponding targeted and pre-immunotherapy genetic testing before receiving immune checkpoint inhibitor therapy, and the results suggested that the PD-1 positivity rate was 100% and 100% in the two groups, respectively, which was consistent with the positive expression of pMMR/MSS.

2.3. Observation indexes

The efficacy, adverse reactions, and survival of both groups were observed. The criteria for determining the efficacy: (1) Complete remission (CR): Complete disappearance of tumor cells confirmed by pathological examination; (2) Partial remission (PR): Shrinkage of tumor foci by > 30%; (3) Stable (SD): No change in the volume of foci; (4) Progression (PD): Increase in the size of tumor foci.

2.4. Statistical methods

All data were statistically analyzed using SPSS 21.0 software. The count data were analyzed by χ^2 test, and $P < 0.05$ was regarded as a statistically significant difference.

3. Results

3.1. Efficacy of the two groups of patients

The efficacy of the observation group and the control group was evaluated according to the RECIST1.3 standard after 3 to 5 cycles of chemotherapy. Among them, the complete remission rate of the control group was 1 case, partial remission was 4 cases, 9 cases were stable, and 7 cases progressed, and the total remission rate [(complete remission + partial remission) ÷ total cases × 100%] was 23.81%, while the complete remission rate of the observation group was 4 cases, partial remission was 8 cases, 5 cases were stable, and 4 cases progressed, and the total remission rate was 57.14%. The difference between the two groups was statistically significant ($P < 0.05$), as shown in Table 1.

Table 1. Comparison of efficacy between the two groups

Groups	Complete remission	Partial remission	Stable	Progress	Overall remission rate
Control group ($n = 21$)	1	4	9	7	5 (23.81)
Observation group ($n = 21$)	4	8	5	4	12 (57.14)
χ^2					4.842
P					< 0.05

3.2. Adverse reactions

A total of 14 cases of adverse reactions occurred in the two groups, with an incidence rate of 33.33% (14/42). Among them, 2 patients were admitted to the hospital for aggravation of fatigue with mild low fever, diagnosed as G-CSF-associated granulocytopenia; 2 patients showed neutropenia, which was considered to be caused by G-CSF; another 2 patients discontinued the drug due to severe diarrhea, and continued to be treated with the drug after adjusting the dosage; the remaining 8 patients only showed minor adverse reactions such as fatigue and nausea, and all patients could tolerate the drug treatment without life-threatening serious adverse reactions. All patients could tolerate the drug treatment and no life-threatening serious adverse reactions occurred.

3.3. Survival

The median follow-up time of the two groups was 6 months, and the overall survival rates of the observation group and the control group were 71.43% and 47.62%, respectively. The survival rate of the observation group was higher than that of the control group, but the difference was not statistically significant ($P > 0.05$), as shown in Table 2.

Table 2. Comparison of survival between the two groups

Groups	Survival	Death
Control group ($n = 21$)	10 (47.62)	11 (52.38)
Observation group ($n = 21$)	15 (71.43)	6 (28.57)
χ^2		2.471
P		0.116

4. Discussion

Currently, the internationally recognized treatments for colorectal cancer include surgery, radiotherapy, and chemotherapy. Chemotherapy is the first-line or second-line standard treatment for patients with advanced colorectal cancer, but due to the presence of a large number of cancer stem cells (CSC) in the tumor tissues, which leads to the poor effect of chemotherapy, for advanced patients who are unable to undergo surgical resection, chemotherapy-based combined with targeted drugs can increase the therapeutic efficacy and improve the survival period. In recent years, immune checkpoint inhibitors targeting different mechanisms have made progress in clinical studies one after another, but there are fewer domestic and international studies reported on regorafenib alone and in combination with other drugs. Among them, Kong et al. [3] pointed out that the anti-PD-1 monoclonal antibody pembrolizumab has been approved by the FDA for use in patients with metastatic colorectal cancer who have been previously treated with positive PD-L1 expression, and regorafenib has a certain anti-tumor effect in patients with excessive activation of immune checkpoints. Li et al. [4] showed that regorafenib combined with PD-1 monoclonal antibody has good efficacy in the treatment of patients with advanced colon cancer, but its specific mechanism of action is still unclear. Lu [5] believed that regorafenib plays an anti-tumor role by inhibiting the PI3K/Akt/mTOR signaling pathway, which plays an important role in the proliferation of tumors, and when the cancer cells lose the normal "brakes," they will lose control of their growth, and regorafenib can block this pathway, thus inhibiting the growth of advanced colon cancer. Regorafenib can block this pathway, thus inhibiting tumor growth. At the same time, An and colleagues [6] pointed out that regorafenib can also induce apoptosis by inhibiting the expression of genes such as c-Met, HGF, and EGFR, and promote apoptosis by up-regulating the anti-apoptotic ability of tumor cells. In addition, regorafenib increases MHC-II molecules on the surface of cancer cells and induces the production of programmed death ligand-1 (PD-L1) in cancer cells, which allows cancer cells to evade recognition by the immune system. Thus, regorafenib may synergistically kill tumor cells through the above multiple pathways.

Yan [7] showed that regorafenib not only directly binds to PD-L1 protein and inhibits its mediated T-cell inactivation, but also inhibits TIGIT protein in tumor cells and reduces the infiltration of lymphocytes into tumor cells. In addition, Gao et al. [8] found that regorafenib can also block the JAK2/STAT3 signaling pathway, resulting in the inactivation of the JAK/STAT signaling pathway, thus reducing the migration and invasion ability of cancer cells. regorafenib can inhibit the proliferation, migration, and invasion of tumor cells through a variety of mechanisms, and thus achieve anti-tumor effects.

It is worth noting that although regorafenib as a small molecule inhibitor has good clinical efficacy in solid tumors, it has a high toxicity response and is only suitable for patients with stable control of the underlying disease such as high leukocytes, hypertension, and diabetes mellitus [9]. Therefore, the choice of using regorafenib under the premise of stable control of the underlying disease ensures the effectiveness of the treatment while taking into account the safety of patients. Regorafenib has shown good efficacy in both inhibiting tumor growth and inducing apoptosis with an excellent safety profile, which can be used as one

of the effective drugs for the treatment of advanced colorectal cancer [10]. However, clinical trial data on its combination with immunosuppressants (e.g., anti-PD-1 monoclonal antibody) for the treatment of advanced colorectal cancer are lacking and need to be confirmed by further studies.

In this study, the overall remission rate of the control group was 23.81%, and the overall remission rate of the observation group was 57.14%, and the difference between the two groups was statistically significant ($P < 0.05$); a total of 14 cases of adverse reactions occurred in the patients of the two groups, with an incidence rate of 33.33% (14/42); and the overall survival rate of the observation and control groups was 71.43% and 47.62%, respectively. The survival rate of the observation group was higher than that of the control group, but the difference was not statistically significant ($P > 0.05$). It indicates that regorafenib combined with immune checkpoint inhibitors can achieve better efficacy, a higher overall remission rate, and a greater survival rate. In addition, the occurrence of adverse drug reactions can be reduced by the combination treatment mode. In this study, patients with pMMR/MSS-type colorectal cancer who had recurrence after preoperative radiotherapy were compared, and it was found that regorafenib combined with PD-1 monoclonal antibody could significantly prolong the survival of patients, and the safety was good, with no significant adverse reactions occurring. It should be noted that the patients selected in this study were all patients with advanced tumors and clear clinical needs, but the clinical trial did not screen all patients, so it could not be directly compared with other published studies, and could only be used as an observational analysis.

In conclusion, for patients with advanced colorectal cancer of the pMMR/MSS type, regorafenib combined with immune checkpoint inhibitors has obvious advantages over monotherapy in terms of safety and efficacy and is expected to be the first-line treatment option for patients with this type of advanced colorectal cancer.

Disclosure statement

The authors declare no conflict of interest.

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