Original Article

Efficacy and safety of regorafenib in the treatment of metastatic colorectal cancer: a retrospective cohort study

Hao Yan[1#], Jindong Liu[1#], Yifan Zhang[1], Shuo Chen[2], Jing Xu[3], Dandan Gao[4], Haipeng Li[4], Xinyue Fang[5], Yu Wang[4], Huaqing Wang[1], Hui Wang[1]

[1]Department of Oncology, Tianjin Union Medical Center, Tianjin, China; [2]Department of Proctology, Tianjin Union Medical Center, Tianjin, China; [3]Department of Surgery, Tianjin Union Medical Center, Tianjin, China; [4]School of Integrative Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China; [5]NanKai University School of Medicine, Tianjin, China

Contributions: (I) Conception and design: Hui Wang, H Yan; (II) Administrative support: Hui Wang; (III) Provision of study materials or patients: J Liu, Y Zhang, S Chen, J Xu; (IV) Collection and assembly of data: X Fang, Y Wang; (V) Data analysis and interpretation: D Gao, H Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Hui Wang, MD. Department of Oncology, Tianjin Union Medical Center, No. 190 Jiyuan Road, Hongqiao District, Tianjin 300122, China. Email: wanghui2@umc.net.cn.

Background: The majority of studies of regorafenib now were small-sample and single-arm, which potentially limits the strength of evidence. We conduct the study to identify the efficacy and safety of regorafenib for patients with metastatic colorectal cancer (mCRC) in real-world applications.

Methods: mCRC patients who underwent regorafenib second line or post-second line treatment with at least one assessable lesion were analyzed. Patients received different doses of regorafenib and different combination regimens. The patients were followed up with laboratory tests and imaging examinations every 3 months to evaluate the efficacy and adverse events (AEs). The primary endpoint of this study was median overall survival (mOS), and the secondary endpoints were median progression-free survival (mPFS), the objective response rate (ORR), the disease control rate (DCR), and AEs.

Results: A total of 77 patients (45 males and 32 females, aged 58.80±11.65 years) were enrolled in the study. Most primary tumors were located in the rectum (59.74%), and the vast majority of tumors (89.62%) had an adenocarcinoma histological type. The 77 patients had an mOS of 17.8 months, a progression-free survival (PFS) of 4.63 months, an ORR of 6.76%, and a DCR of 55.41%. Patients underwent regorafenib third-line therapy had significantly higher overall survival (OS) than those underwent regorafenib post- third-line treatment (P=0.03). The neutrophil to lymphocyte ratio (NLR) was an independent factor affecting the OS of the mCRC patients [hazard ratio (HR) =1.12, P=0.03]. In both univariate and multivariate analyses, discontinued use of regorafenib after progression reduced patients' PFS (HR =3.07, P<0.001; HR =2.78, P=0.007). In terms of the tolerated dose, patients receiving 120 mg regorafenib had the longest OS numbers, but there was no statistical difference. We analyzed the effect of the baseline NLR on the OS of patients receiving regorafenib combined with immunotherapy, and found that the NLR ratio cut-off value was 4.4, and patients with a NLR ratio ≤4.4 benefited significantly in terms of OS (P=0.03). The AEs included 21 (27.27%) cases of hand and foot skin reaction, 15 (19.48%) cases of fatigue, 9 (11.69%) cases of pain, 9 (11.69%) cases of nausea, 9 (11.69%) cases of fever, 9 (11.69%) cases of cough, and so on.

Conclusions: Regorafenib is relatively effective and safe as a third-line and posterior treatment of mCRC. Patients underwent regorafenib third-line therapy had longer OS than those underwent regorafenib post-third-line treatment. Moreover, PFS benefits can still be obtained by continuing regorafenib treatment after progression. Grade 1–2 AEs were common, but these were usually tolerated by most patients.

Keywords: Regorafenib; metastatic colorectal cancer (mCRC); retrospective study; efficacy; safety

Submitted Mar 18, 2024. Accepted for publication May 22, 2024. Published online Jun 18, 2024.
doi: 10.21037/jgo-24-180
View this article at: https://dx.doi.org/10.21037/jgo-24-180

Introduction

Colorectal cancer (CRC) is a common malignant tumor of the digestive system. According to data released by the International Agency for Research on Cancer of the World Health Organization in 2020, CRC ranked second and fifth in terms of incidence and mortality, respectively, among all malignant tumors in China (1). The disease has an insidious onset, with no evident specificity in the early stage, and most patients are already in the middle to late stages at the time of diagnosis. About 20% of patients have metastasis at the time of diagnosis, and about 50% of patients will develop metastasis during the disease course (2). Currently, surgery is still the only radical treatment for early CRC.

Patients with metastatic colorectal cancer (mCRC) have a poor prognosis, and usually have lost the chance of radical surgery. First- and second-line systemic treatments of mCRC are still based on chemotherapy, and standard chemotherapeutic regimens usually combine irinotecan, calcium folinate, fluorouracil, and oxaliplatin (FOLFIRI/FOLFOX) (3); however, chemotherapeutic regimens are characterized by the deficiencies of drug resistance, systemic toxicity, a low disease remission rate, and poor efficacy. In recent years, the combination of radiation therapy, targeted therapy, and immunotherapy has dramatically improved the median overall survival (mOS) of mCRC patients, which can reach 30 months (4).

However, drug resistance and disease progression are still unavoidable, and many mCRC patients, in whom first- and second-line treatments fail, need to undergo third-line treatments. The third-line drugs recommended in China's diagnostic and therapeutic specifications mainly include regorafenib and fruquintinib (5). Regorafenib is the first small-molecule multikinase inhibitor approved for mCRC treatment (6). The large phase-III randomized controlled CONCUR study (7), which was conducted in Asia, showed a significant OS benefit in advanced mCRC patients who received a third-line treatment of regorafenib compared to those who received a placebo, with a mOS of 8.8 months and a median progression-free survival (mPFS) of 3.2 months for regorafenib group. Regorafenib is a small molecule inhibitor of various kinases. Regorafenib can normalize tumor blood vessels through the inhibition of neovascularization (e.g., VEGFR1-3, FGFR1-2, and PDGFRα/β), inhibit tumor cell proliferation and migration (e.g., KIT, RET, and RAF), and improve the tumor immune microenvironment (CSF1R). In addition, improvement in systemic inflammation via regulating immune cell function is one of several potential treatment mechanisms for regorafenib (8,9).

Compared with the limited efficacy of regorafenib monotherapy, the diversity of regorafenib's target provided the foundation for the feasibility of a combination regimen (10). Combining regorafenib with immune

Highlight box

Key findings

- Regorafenib is considered safe and effective as a third-line and subsequent treatment for patients with metastatic colorectal cancer (mCRC). Patients who underwent regorafenib as a third-line therapy experienced longer overall survival (OS) than those who received regorafenib after third-line treatment. Furthermore, continuing regorafenib treatment after disease progression can still provide progression-free survival (PFS) benefits. Among patients, those who received 120 mg dose of regorafenib achieved the longest OS, although this difference was not statistically significant.

What is known, and what is new?

- The mCRC patients who received a third-line regorafenib treatment demonstrated a median overall survival (mOS) of 8.8 months and a median progression-free survival (mPFS) of 3.2 months, indicating significantly better OS compared to those who received a placebo.
- Compared to the monotherapy, combined immunotherapy, combined chemotherapy, and combined radiotherapy groups, the regorafenib combined with immunotherapy group had the longest mPFS of 7.98 months (the difference among the groups was not statistically significant), and the mOS of these patients was associated with the neutrophil to lymphocyte ratio. Additionally, the mPFS of patients who continued treatment with regorafenib after progression was prolonged compared to those who discontinued treatment.

What is the implication, and what should change now?

- An initial dose of 120 mg regorafenib may be considered suitable for mCRC patients.
- Combination therapy in the subsequent-line treatment of mCRC has shown favorable benefits in terms of mOS and mPFS.
- In selecting treatments, consideration should be given to the clinical characteristics and molecular classification of the tumor.

checkpoint inhibitors has received more attention in recent years due to its feasibility and manageable safety profile (11). The REGONIVO study (12) pioneered target-immunity combinations for intestinal cancer, and reported an ORR of 36% and an mPFS of 7.9 months, but the mOS had not been reached. A retrospective study (13) showed that patients with advanced mCRC who received regorafenib combination chemotherapy after the failure of standard therapy achieved a mOS of 15.9 months, which represents a significant benefit compared to that achieved by patients who receive regorafenib alone (P=0.03). In addition, a real-world study reported (14) that patients who received regorafenib combined with local therapy (i.e., hepatic artery infusion chemotherapy) for the treatment of mCRC liver metastasis, in whom standard chemotherapy had failed, had a mPFS of 10.8 months and a mOS of 22.2 months. One recent nonrandomized clinical trial indicated that the combination of regorafenib, ipilimumab, and nivolumab showed significant clinical activity in patients with patients with microsatellite-stable colorectal cancer and disease progression with prior chemotherapy (15). A retrospective analysis proved the combination of regorafenib plus anti-PD-1 antibodies has reliable security (16).

While the above studies have shown the therapeutic potential of regorafenib, the majority of studies were small-sample and single-arm, which potentially limits the strength of evidence. There was a considerable discordance of available clinical data (17), which might be partially explained by the vast heterogeneity of patient characteristics and geographic regions. In terms of security, Further studies are needed to clarify the relationship between dose and the probability of adverse drug reactions (mainly hand-foot-skin reactions) (18).

This study retrospectively examined the efficacy and safety of regorafenib in mCRC patients treated at Tianjin Union Medical Center in recent years to provide more data for the efficacy and safety of regorafenib and combination of regorafenib and other treatments. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-180/rc).

Methods

Inclusion and exclusion criteria

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) meet the Chinese Colorectal Cancer Diagnostic and Treatment Criteria and have pathologically confirmed CRC (6); (II) be unable to undergo radical surgical treatment for mCRC; (III) be aged 18–80 years; (IV) have previously received at least one line of a standard treatment regimen that had failed; (V) have been treated with regorafenib either alone or in combination with other treatments; (VI) have at least one assessable lesion; (VII) have acceptable cardiac, hepatic and renal function and be able to tolerate the treatment; and (VIII) have complete clinical data and relevant outcome indicators.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) were pregnant and/or breastfeeding; (II) had an Eastern Cooperative Oncology Group (ECOG) score ≥3; (III) had a psychiatric disorder and/or could not cooperate with the treatment; (IV) had other malignant tumors; (V) had regorafenib treatment shorter than 1 treatment cycle; and/or (VI) who's clinical data were missing.

General information and follow-up procedures

We retrospectively analyzed the clinical data of mCRC patients treated with regorafenib at Tianjin Union Medical Center from December 2018 to December 2022. The patients were followed up with laboratory tests and imaging examinations every 3 months to evaluate the efficacy until the last follow-up in December 2022 or the patient died. The following data were collected: age, gender, ECOG score, primary tumor site, metastatic site, histology type, differentiation, microsatellite status, sarcoma viral oncogene homolog (*KRAS*) gene mutation status, neuroblastoma RAS viral oncogene homolog (*NRAS*) gene status, murine sarcoma filtration toxin bacterium oncogene homolog B1 (*BRAF*) gene status, history of previous treatment, history of previous targeted drug use, and history of previous immunotherapy. The study was approved by the Medical Ethics Committee of Tianjin Union Medical Center (No. 2023B51), and the patients and/or their immediate family signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Treatment regimens

Patients were treated with regorafenib alone or in combination with other treatments. Regorafenib tablets (Bayer Healthcare GmbH, China National Drug

Administration HJ20171300) were administered at an initial dose of 80, 120, or 160 mg depending on each patient's condition, with weekly adjustments of 40 mg to a maximum of 160 mg according to each patient's tolerance. Four weeks of treatment represented one treatment cycle. The drug was administered orally once daily on days 1–21 and discontinued on days 22–28 of one treatment cycle until disease progression, death, or intolerable AEs.

Efficacy and safety outcomes

Tumor response was classified as complete remission (CR), partial remission (PR), progressive disease (PD), or stable disease (SD) according to the Response Evaluation Criteria In Solid Tumors (RECIST 1.1). The overall effective rate (ORR) was calculated as follows: ORR = (CR + PR)/ total number of cases × 100%. The disease control rate (DCR) was calculated as follows: DCR = (CR + PR + SD)/ total number of cases × 100%. AEs were classified into the following 5 grades according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 5.0): grade 1 is asymptomatic or mild symptoms; grade 2 is moderate; grade 3 is severe; grade 4 is life-threatening; and grade 5 is death. The frequency of AEs, OS, and PFS were observed.

Statistical analysis

SAS statistical software (version 9.4, SAS Institute Inc., Cary, USA) was used to analyze the data. Efficacy and safety outcomes were analyzed using descriptive statistical methods, including mean value, median value, standard deviation, and percentage. Univariate analysis of different influencing factors for PFS an OS was performed by Kaplan-Meier (K-M) survival analysis, the mOS time was calculated, and survival curves were plotted and compared using the log-rank test. Factors with a P value <0.1 in the univariate analysis were included in the Cox proportional risk model for the multivariate analysis. Statistical tests were two-sided, and a P value <0.05 indicated a statistically significant difference.

Results

Baseline data

A total of 77 patients (45 males and 32 females, aged 58.80±11.65 years) were enrolled in the study. Three patients were lost to follow-up at different stages of the experiment. The majority of the patients received third- and subsequent lines of treatment; 45 underwent third-line therapy, 31 underwent posterior third-line therapy, and one received regorafenib as a second-line treatment. Most patients were in good general condition; 71 (92.21%) patients had an ECOG score of 1. Most primary tumors were located in the rectum (59.74%), and the vast majority of tumors (89.62%) had an adenocarcinoma histological type. Most patients had liver (45.45%) and lung metastases (48.05%); peritoneal metastases were present in 17.8% of the patients. The vast majority of patients had a stable microsatellite status (97.4%), but the RAS/RAF gene status was unknown in a majority of the patients. Of the patients, 79.22% had previously received surgical treatment, 48.05% had previously received an anti-VEGF monoclonal antibody, and 36.36% had previously received immunotherapy. General patient information is shown in *Table 1*.

Treatment regimens

According to the general condition of the patients and the results of genetic testing and local lesions, most patients needed combination therapy. Thus, 35 of the 77 patients were treated with regorafenib alone, and 42 were treated with a combination of regorafenib and chemotherapy, radiotherapy, or immunotherapy. The best-tolerated dose of regorafenib was 120 mg in both the monotherapy and combination therapy groups, with few patients discontinuing the drug because of AEs. The dosing profile is shown in *Table 2*.

Results of solid tumor efficacy evaluation

The ORR rate of the 74 patients was 6.76% and the DCR rate was 55.41%. The monotherapy group had a relatively good ORR (6.06%) and DCR (60%). The regorafenib-radiotherapy combination group had the best ORR (16.67%). No patients in the regorafenib-immunotherapy combination group and regorafenib-chemotherapy combination group achieved objective remission. Additionally, the highest DCR rate among the combined treatment groups was 83.33% for regorafenib-chemotherapy combination group, followed by 44.44% for regorafenib-radiotherapy combination group, and 22.22% for regorafenib-immunotherapy combination group. The overall mPFS of the 74 patients was 4.63 months, and the mOS was 17.8 months.

Table 1 Patient, tumor, and treatment characteristics

Characteristic	Values
Sex	
Male	45 (58.44)
Female	32 (41.56)
ECOG score	
ECOG 1	71 (92.21)
ECOG 2	6 (7.79)
Primary tumor site	
Rectum	46 (59.74)
Left colon	22 (28.57)
Right colon	4 (5.19)
Unknown	5 (6.49)
Histologic type	
Adenocarcinoma	69 (89.62)
Mucinous adenocarcinoma	4 (5.19)
Unknown	4 (5.19)
Differentiation	
Highly differentiated	4 (5.19)
Moderately differentiated	24 (31.17)
Low differentiation	10 (12.99)
High and medium differentiation	3 (3.90)
Medium, low differentiation	24 (31.17)
Unknown	12 (15.58)
Metastasis	
Lung	37 (48.05)
Liver	35 (45.45)
Peritoneal	13 (16.88)
Microsatellite status	
pMMR	75 (97.4)
dMMR	2 (2.6)
KRAS	
KRAS (wild-type)	21 (27.27)
KRAS (mutant)	11 (14.29)
KRAS (unknown)	45 (58.44)
NRAS	
NRAS (wild-type)	18 (23.38)
NRAS (mutant)	2 (2.60)
NRAS (unknown)	57 (74.03)
BRAF	
BRAF V600E (wild-type)	5 (6.49)
BRAF V600E (mutant)	2 (2.60)
BRAF V600E (unknown)	70 (90.91)
Prior therapy	
Surgery	61 (79.22)
Neoadjuvant therapy	19 (24.68)
Prior targeted medications	
Anti-*VEGF* monoclonal antibody	37 (48.05)
Anti-*EGFR* monoclonal antibody	10 (12.99)
TKI	4 (5.19)
Unknown	26 (33.77)
Prior immunotherapy	28 (36.36)

Data are shown as n (%). ECOG, Eastern Cooperative Oncology Group; pMMR, perfect-mismatch repair; dMMR, defect-mismatch repair; *VEGF*, vascular endothelial growth factor; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Analysis of the factors affecting patient prognosis

Univariate analysis was performed by K-M survival analysis to determine the correlation of the baseline characteristics and treatment factors with PFS and OS. The results of the univariate analysis showed that the primary site (right-sided colon), degree of differentiation (low differentiation), and discontinuation due to AEs and the NLR ratio were relatively significant factors affecting PFS ($0.05<P<0.1$). The NLR was an independent factor affecting the OS of the mCRC patients (P=0.03). The results of the multivariate analysis showed that hypofractionation (P=0.02, 95% CI: 1.2320–21.7270) and drug discontinuation (P=0.007, 95% CI: 1.3270–5.8400) were factors affecting the PFS of the mCRC patients. The univariate analysis of OS revealed that only one significant factor affected PFS; thus, a multivariate

Table 2 Medication utilization

Mode of treatment	Values
Combined treatment	
Monotherapy	35 (45.45)
Combined immunotherapy	18 (23.38)
Combined chemotherapy	6 (7.79)
Combined radiotherapy	18 (23.38)
Starting dose	
80 mg	3 (3.90)
120 mg	62 (80.52)
160mg	12 (15.58)
Tolerated dose	
80 mg	21 (27.27)
120 mg	49 (63.64)
160mg	7 (9.09)
Drug discontinuation	46 (59.74)

Data are shown as n (%).

analysis was not performed. See *Tables 3*,*4*.

Results of PFS and OS of different metastatic sites

More than half of the mCRC patients had liver metastasis and a poor prognosis. The proportion of liver metastasis in this study was 45.45%. The mPFS of patients with liver metastasis was 12.85 months, and the mOS had not yet been reached; these figures were higher than those reported in a previous study (19). In addition, 48.05% of the patients in this study had lung metastasis, and these patients had an overall mPFS of 8.48 months and an mOS of 16.85 months; these figures are lower than those previously reported in studies examining treatment regimens of regorafenib with triprizumab (20). This may be because patients in real-world studies have more complex situations and worse baselines than those patients in clinic trials. Two patients with lung metastasis in this study also had brain or bone metastasis.

Peritoneal metastasis is a common type of metastasis in CRC and has a poorer prognosis than other types of

Table 3 Univariate analysis for OS and PFS

Factors	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.9940	0.920–1.0160	0.57	0.9870	0.9590–1.0160	0.37
Male	0.7860	0.4590–1.3470	0.38	0.8020	0.3940–1.6320	0.54
ECOG 1	1.1020	0.3950–3.0700	0.85	0.7850	0.2350–2.6190	0.69
Primary site						
Rectum	3.0680	0.4180–22.5150	0.27	1,198,460.0000	0.0000–NE	0.99
Left colon	3.8790	0.5160–29.1730	0.19	1,474,109.0000	0.0000–NE	0.99
Right colon	9.8590	1.0020–97.0340	0.05*	2,128,572.0000	0.0000–NE	0.99
Histologic type adenocarcinoma	1.8120	0.4400–7.4700	0.41	0.7570	0.2260–2.5340	0.65
Degree of differentiation						
High	3.1290	0.9890–9.8960	0.05	1.9760	0.4110–9.4940	0.40
Medium	1.3010	0.6450–2.6230	0.46	1.2100	0.4800–3.0540	0.69
Low	2.5540	1.0370–6.2900	0.04*	1.5180	0.4520–5.0990	0.50
Medium, low	0.7860	0.1770–3.4890	0.75	0.3530	0.0430–2.8880	0.33

Table 3 (*continued*)

Table 3 (*continued*)

Factors	PFS			OS		
	HR	95% CI	P value	HR	95% CI	P value
Metastatic site						
Lung	0.9890	0.5810–1.6820	0.97	1.4440	0.7080–2.9430	0.31
Liver	1.2370	0.7230–2.1140	0.44	0.5370	0.2530–1.1380	0.10
Peritoneum	0.7760	0.3640–1.6530	0.51	1.2320	0.4650–3.2600	0.67
Microsatellite pMMR	1.4370	0.1960–10.5170	0.72	0.0000	0.0000–NE	0.99
RAS						
KRAS wild type	0.6780	0.2890–1.5940	0.37	0.3940	0.1040–1.4910	0.17
NRAS wild type	0.3840	0.0420–3.4790	0.39	1,422,744.0000	0.0000–NE	>0.99
BRAF wild type	1.0290	0.0920–11.4810	0.98	–	–	–
Prior therapy						
Surgery	0.8300	0.4440–1.5500	0.56	0.7150	0.2860–1.7870	0.47
Neoadjuvant therapy	0.5510	0.2230–1.3640	0.20	0.3740	0.1120–1.2420	0.11
Prior medications						
Anti-*VEGF* monoclonal antibody	1.0740	0.6270–1.8410	0.79	1.2300	0.6120–2.4740	0.56
Anti-*EGFR* monoclonal antibody	1.0870	0.5100–2.3150	0.83	0.7380	0.2560–2.1220	0.57
TKI	0.5600	0.0760–4.1010	0.57	2.8340	0.3520–22.8200	0.33
Prior immunotherapy	0.7270	0.4050–1.3060	0.29	1.2130	0.5810–2.5310	0.61
Combination immunotherapy	0.8500	0.4320–1.6690	0.64	1.4080	0.6110–3.2470	0.42
Chemotherapy	1.2650	0.4830–3.3120	0.63	1.2680	0.3440–4.6810	0.72
Radiotherapy	0.6340	0.3110–1.2920	0.21	0.7180	0.2660–1.9400	0.51
Starting dose						
80 mg	3.5850	0.7350–17.5000	0.11	3.8040	0.4030–35.9060	0.24
120 mg	1.4100	0.6600–3.0130	0.37	1.9570	0.6610–5.7920	0.23
Tolerated dose						
80 mg	1.0230	0.3960–2.6390	0.96	0.7680	0.2550–2.3130	0.64
120 mg	0.7200	0.3000–1.7270	0.46	0.5520	0.2090–1.4580	0.23
Drug discontinuation	3.0710	1.6420–5.7440	<0.001*	1.3590	0.6560–2.8150	0.41
Adverse events	2.1430	0.8770–5.2380	0.09	1.3030	0.3000–5.6690	0.72
Disease progression	1.1690	0.5700–2.3970	0.67	0.5440	0.2060–1.4390	0.22
Other reasons	0.7000	0.3780–1.2940	0.25	1.4620	0.6260–3.4180	0.38
NLR	1.0770	0.9910–1.1700	0.08*	1.1220	1.0130–1.2420	0.03

*, included in multivariate analysis. OS, overall survival; PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; pMMR, perfect-mismatch repair; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NLR, neutrophil to lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Table 4 Multivariate analysis for PFS

Factors	HR	95% CI	P value
Primary site			
Rectum	534,015.6000	0.0000–NE	0.99
Left colon	1,199,421.0000	0.0000–NE	0.99
Right colon	3,073,342.0000	0.0000–NE	0.99
Degree of differentiation			
High	5.1740	1.2320–21.7270	0.02*
Medium	1.3410	0.6020–2.9890	0.47
Low	2.4070	0.8350–6.9380	0.10
Medium, low	3.8990	0.4800–31.6920	0.20
Drug discontinuation	2.7840	1.3270–5.8400	0.007*
Adverse event discontinuation	1.0060	0.2270–4.4600	0.99
NLR	1.0930	0.9850–1.2130	0.10

*, significant P value in multivariate test (P<0.05). PFS, progression-free survival; NLR, neutrophil to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; NE, not estimable.

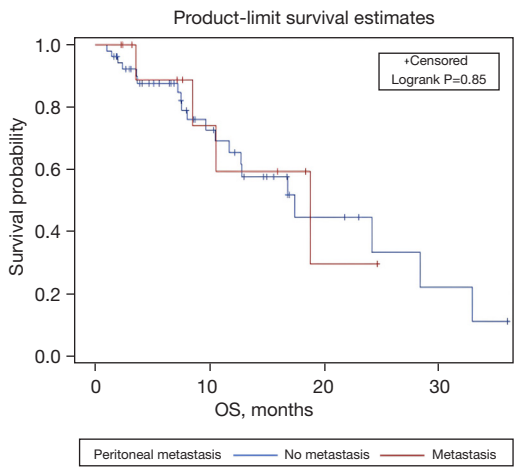

Figure 1 Kaplan-Meier curves for OS of patients with and without peritoneal metastatic. OS, overall survival.

metastases. With the gradual recognition of the treatment modalities of tumor cytoreduction surgery (CRS) and heat intraperitoneal perfusion chemotherapy (HIPEC) by surgeons, as well as the application of anti-tumor targeting drugs and immune drugs, the prognosis of CRC patients with peritoneal metastasis has greatly improved. However, there are still many challenges and controversies in the diagnosis and treatment of CRC patients with peritoneal metastasis, and the median OS of such patients after diagnosis is only 6–9 months (21). In this study, 13 patients (17.81%) developed peritoneal metastasis, and had an overall OS of 18.83 months (*Figure 1*). This excellent result may be due to our personalized treatment for patients with different baseline conditions. At the same time, regorafenib, as a multi-target small molecule inhibitor of various kinases, has a good effect on patients with complex situations such as peritoneal metastasis.

Results of PFS and OS in different treatment lines

Among the 77 patients, 45 (58.44%) underwent regorafenib third-line therapy, and 31 (40.26%) underwent regorafenib post- third-line treatment. The analysis showed that the mPFS of the third-line treatment group was 7.16 months (95% CI: 3.29–9.17), and the mOS was 19.02 months (95% CI: 17.41–28.42). The mPFS of the post- third-line treatment group was 8.05 months (95% CI: 3.38–12.75), and the mOS was 10.55 months (95% CI: 8.05–12.85). A log-rank test showed a statistically significant difference in the OS between the two groups (P=0.03). See *Figure 2*.

Analysis of PFS and OS of different treatment regimens

The results showed that the mPFS of the monotherapy group, regorafenib-immunotherapy combination group, regorafenib-chemotherapy combination group, and

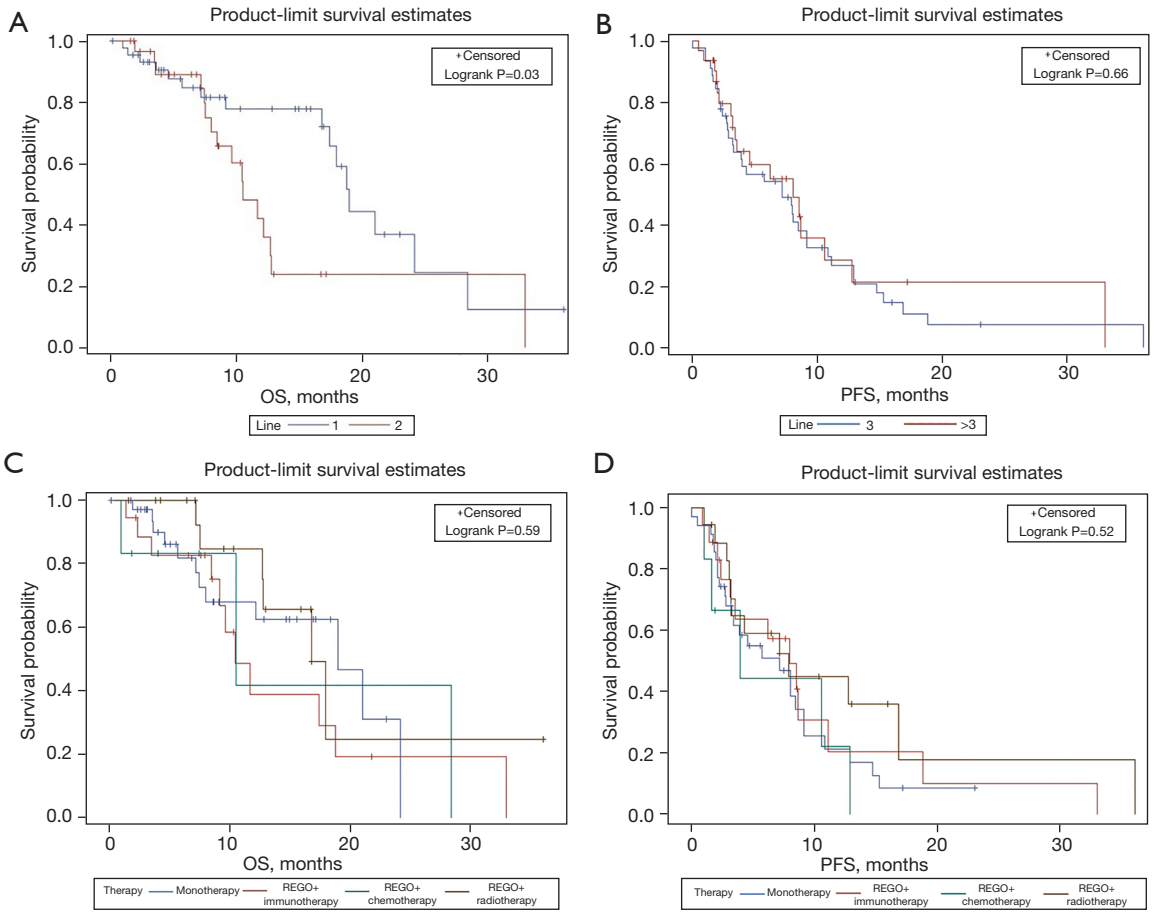

Figure 2 Kaplan-Meier curves for PFS and OS of different treatment lines (A,B) and different treatment regimen groups (C,D). OS, overall survival; PFS, progression-free survival; REGO, regorafenib.

regorafenib-radiotherapy combination group was 7.16 (95% CI: 2.79–9.13), 7.98 (95% CI: 2.40–11.14), 3.94 (95% CI: 7.16–7.16), and 7.89 (95% CI: 3.06–16.85) months, respectively. The regorafenib-immunotherapy combination group had the longest mPFS, but no statistically significant difference was found among the groups based on the log-rank test (P=0.52). The mOS of the monotherapy group, regorafenib-immunotherapy combination group, regorafenib-chemotherapy combination group, and regorafenib-radiotherapy combination group was 19.02 (95% CI: 8.05–24.21), 10.51 (95% CI: 8.51–18.83), 10.55 (95% CI: 1.05–28.42), and 16.85 [95% CI: 12.75–not applicable (N/A)] months, respectively. The monotherapy group had the longest mOS, but no statistically significant difference was found among the groups based on the log-rank test (P=0.59). See *Figure 2*.

Analysis of PFS and OS at different tolerated doses

The results showed that the mPFS of the 80-, 120-, and 160-mg groups was 3.94 (95% CI: 2.10–8.67), 7.98 (95% CI: 3.91–10.81), and 8.48 (95% CI: 2.00–12.88) months, respectively. The 160-mg group had the longest mPFS, but a log-rank test showed that the difference among the groups was not statistically significant (P=0.46). The mOS of the 80-, 120-, and 160-mg groups was 12.85 (95% CI: 8.05–21.03), 17.41 (95% CI: 12.22–32.95), 10.55 (95% CI: 2.00–28.42) months, respectively. The 120-mg group had the longest mOS, but a log-rank test showed that the difference among the groups was not statistically significant

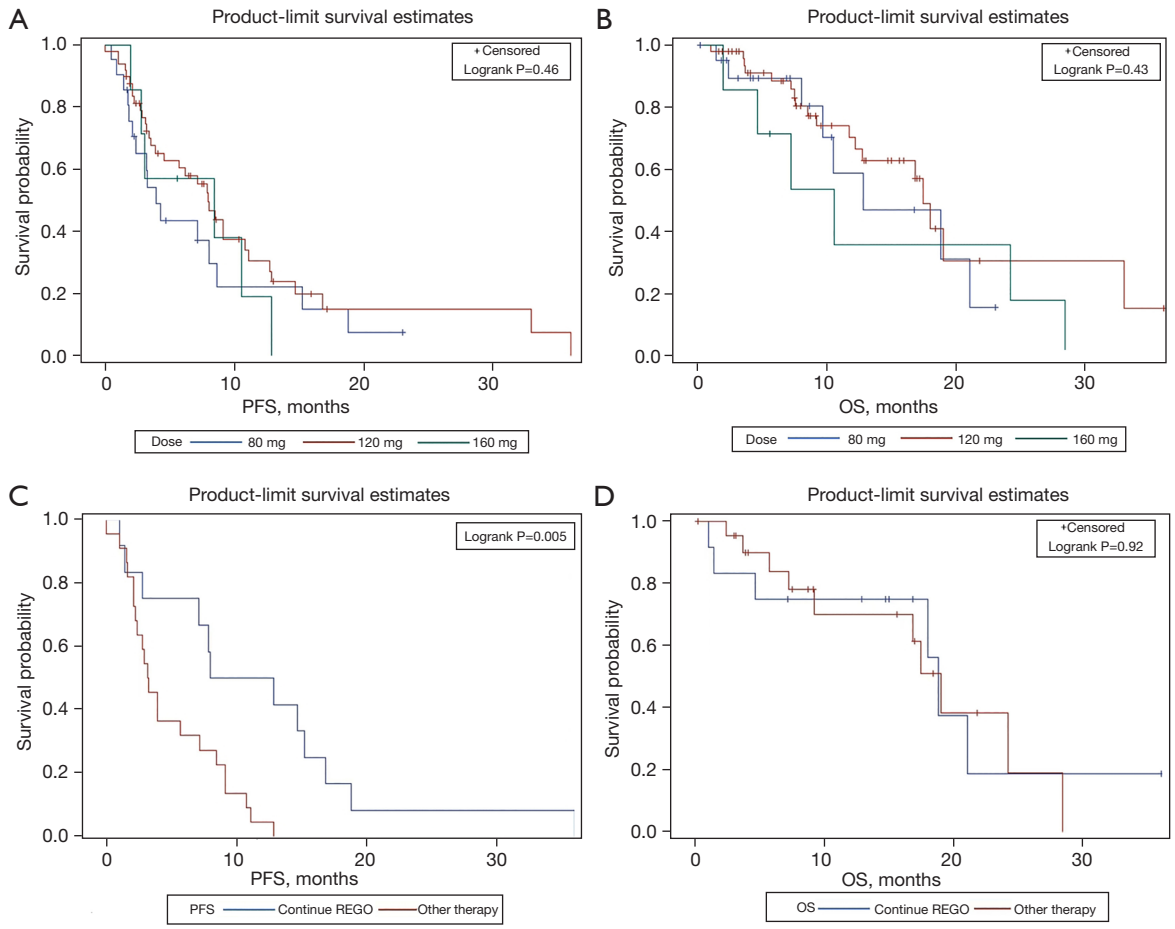

Figure 3 Kaplan-Meier curves for PFS and OS of different tolerated dose groups (A,B) and the continuous use of medication or not (C,D). PFS, progression-free survival; OS, overall survival; REGO, regorafenib.

(P=0.43). See *Figure 3*.

Effect of continuation of anti-vascular therapy after progression on survival

We collected information on medication use after progression in 33 patients, of whom 12 continued to receive regorafenib treatment (either monotherapy or combination therapy), and 22 discontinued regorafenib for other regimens. The mPFS of those that continued to receive regorafenib treatment was statistically different to that of those who discontinued regorafenib treatment [10.45 (95% CI: 1.41–16.85) *vs.* 3.25 (95% CI: 2.10–7.16) months, respectively; P=0.005]. The mOS of the two groups was 18.83 (95% CI: 1.41–not reached) and 19.02 (95% CI: 9.20–28.42) months, respectively. No statistically significant difference was found between continuous treatment group and other regimens group (P=0.92). See *Figure 3*.

Effect of the NLR on the PFS and OS of "regorafenib-immunotherapy combination" therapy

The raw NLR data of 18 patients treated with "regorafenib-immunotherapy combination" therapy were analyzed, and the NLR cut-off value for PFS was 2.4. The mPFS of the NLR ≤2.4 and NLR >2.4 groups was 14.98 (95% CI: 7.98–32.95) and 3.55 (95% CI: 2.10–32.95) months, respectively, and the difference between the two groups was statistically significant based on the log-rank test (P=0.02). The NLR cut-off value for OS was 4.4. The mOS of the NLR ≤4.4 and NLR >4.4 groups was 17.41 (95% CI: 2.40–32.95) and 9.20 (95% CI: 1.41–10.51) months, respectively, and the difference between the two groups was statistically significant based on the log-rank test (P=0.03). See *Figure 4*.

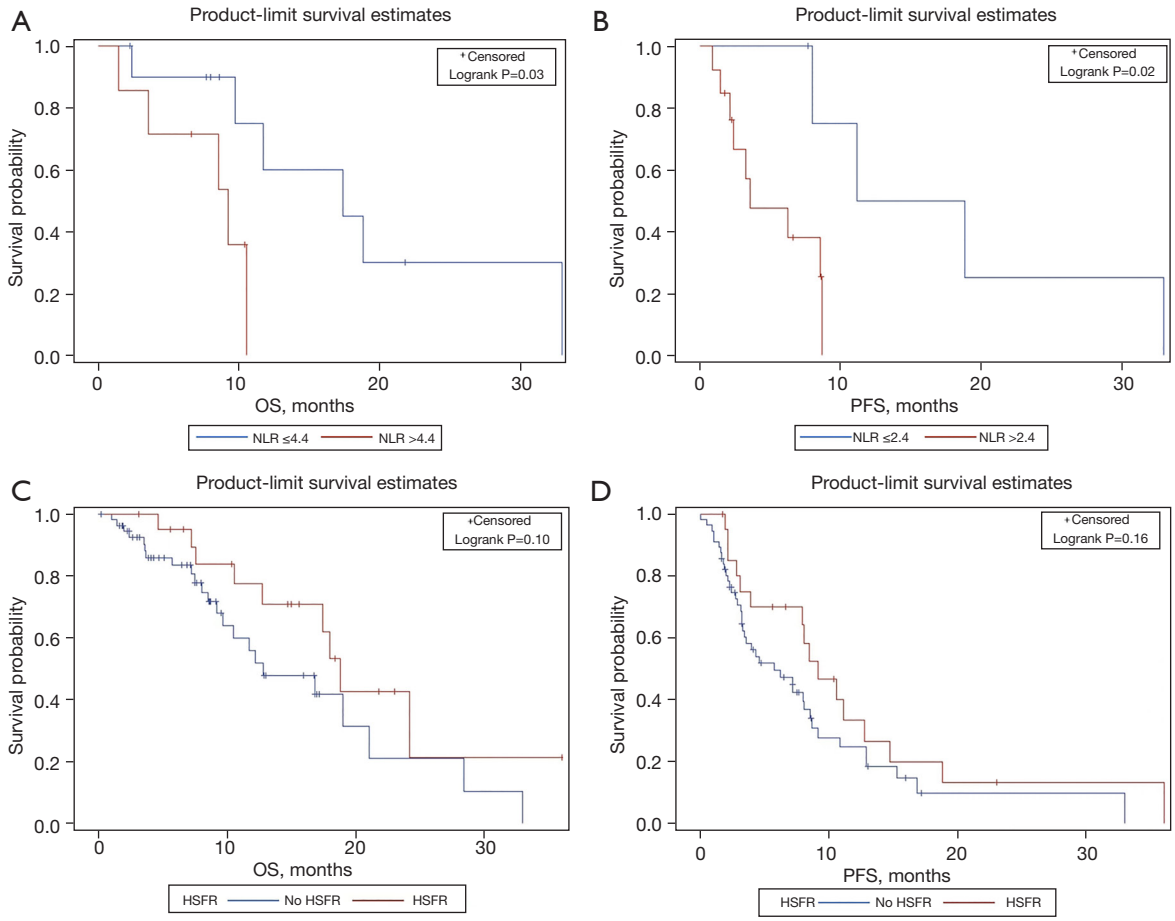

Figure 4 Kaplan-Meier curves for PFS and OS of different NLR ratio groups (A,B) and whether or not HSFRs occurred (C,D). OS, overall survival; PFS, progression-free survival; NLR, neutrophil to lymphocyte ratio; HSFRs, hand-foot skin reactions.

Safety

Overall AE occurrences

In total, 185 AEs were observed in the 77 patients, of which hand-foot skin reactions (HSFRs) had the highest incidence (21 or 27.27%), followed by weakness (19.48%), nausea (11.69%), fever (11.69%), hypertension (11.69%), cough (11.69%), and pain (11.69%). See *Table 5*.

Occurrence of grade ≥3 AEs

In total, 6 patients (7.79%) developed a grade ≥3 AE, of whom two patients developed skin and subcutaneous tissue diseases, one patient developed an infection or infestation disease, one patient developed a respiratory, thoracic, or mediastinal disease, one patient developed a gastrointestinal disease, and one patient developed a hepatobiliary disease.

Prognostic effect of the occurrence of HSFRs

We further analyzed the survival of patients who developed HSFRs versus those who did not, and we found that there was a trend towards prolonged mPFS in patients who developed HSFRs compared to those who did not [9.17 (95% CI: 3.06–12.75) *vs.* 5.72 (95% CI: 3.22–8.51) months, P=0.16]. The mOS of patients with HSFRs also tended to be prolonged compared to those without HSFRs [18.83 (95% CI: 12.75–unattained) *vs.* 12.85 (95% CI: 9.69–21.03) months, P=0.10]. See *Figure 4*.

Discussion

In this study, we retrospectively analyzed the data of 77 patients treated with regorafenib for mCRC. Most of the patients were in good general condition at the baseline (most patients had baseline ECOG scores of 1), and the

Table 5 Occurrence of AEs (more than 5%)

Item	Values
Wheezing	6 (7.79)
Nausea	9 (11.69)
Fever	9 (11.69)
Weakness	15 (19.48)
Abdominal pain	6 (7.79)
Diarrhea	7 (9.09)
Bloating	5 (6.49)
Hypertension	9 (11.69)
Musculoskeletal pain	4 (5.19)
Cough	9 (11.69)
Poor appetite	8 (10.39)
Anemia	5 (6.49)
Hand-foot syndrome	21 (27.27)
Pain	9 (11.69)

Data are shown as n (%). AEs, adverse events.

majority of the patients had adenocarcinoma (89.62%) with good histological typing and differentiation. In relation to the treatment lines, most patients received regorafenib as a third-line treatment (59%), but a small proportion of patients received regorafenib as a second- or post-third-line treatment. Compared with patients who received regorafenib as a post-third-line treatment, those who received regorafenib as the standard third-line treatment had significantly better OS (P=0.02). In relation to the treatment options, most patients chose combination therapy (55%), including combination immunotherapy, combination chemotherapy, and combination local radiotherapy. Few patients stopped using regorafenib due to AEs, which suggests that most patients can tolerate the AEs of regorafenib.

The overall population had an ORR of 6.76% and a DCR of 55.41%. The regorafenib combined with radiotherapy group had the highest ORR (16.67%). Research has shown that regorafenib combined with radiotherapy counteracts radiotherapy-induced nuclear factor-κB (NF-κB) expression and significantly shrinks tumors (22). The overall mPFS and mOS of our study were 4.63 and 17.8 months, respectively, which were higher than those reported in the CONCUR (7) and the CORRECT (23) phase-III clinical studies on regorafenib. The difference in the results may be attributed to the higher efficacy benefit of the combination therapy and the better baseline condition of the patients in our study. At close to 8 months, regorafenib combined with immunotherapy and radiotherapy had the highest mPFS (7.98 and 7.89 months, respectively). Regorafenib alone had the most prolonged OS time (19.02 months), which may be related to the better baseline status of the patients and the lower tumor load. Regorafenib combined with radiotherapy had the second longest mOS time (16.85 months). Patients treated with regorafenib combined with chemotherapy and immunotherapy generally had more systemic lesions, which also affected the overall prognosis of the patients, with a corresponding mOS of 10.55 and 10.51 months, respectively.

In this study, the regorafenib-immunotherapy combination group had a PFS of 7.98 months, which is similar to that reported in the REGNIVO study (13), but higher than that reported in previous studies (20,24,25). However, no advantage was found in terms of OS (which was 10.51 months in the present study). This may be due to the fact that the baseline situations of real-world patients are more complex than those patients in clinic trials, and most of the patients receiving regorafenib combination immunotherapy had peritoneal and lung metastases, which affected the final OS benefit.

In this study, the NLR was further applied to analyze the survival of patients receiving regorafenib combination immunotherapy, and 18 patients treated with regorafenib combination immunotherapy were divided into two groups based on an NLR threshold of 2.4. The mPFS was significantly longer in the low NLR group than the high NLR group (14.98 *vs.* 3.55 months, P=0.02), and the low NLR group had a significantly longer mOS than the high NLR group (17.41 *vs.* 9.20 months, P=0.03). Research has shown (26) that elevated NLR ratios in tumor patients treated with immunotherapy are correlated with a poor prognosis. Tumor-induced neutrophils inhibit cytotoxic T lymphocytes via the production of inducible nitric oxide synthase, which results in tumor immunocompromised function and increases the risk of tumor recurrence and metastasis. A high NLR ratio reflects the imbalance of tumor immunity, which may adversely affect the prognosis of mCRC patients treated with combination immunotherapy. Few studies have examined the prognostic effect of the NLR ratio on intestinal cancer immunotherapy. This study has laid a foundation for future research on the relationship between the NLR ratio and prognosis in intestinal cancer.

The ORR advantage obtained from regorafenib combined with radiotherapy in this study also translated into a survival

advantage. The patients achieved a mPFS of 7.89 months and a mOS of 16.85 months; these figures are superior to those previously reported for regorafenib combined with selective internal irradiation radiotherapy (27) (i.e., a mPFS of 3.7 months and a mOS of 12.1 months). This may be related to the patients' baseline data; the enrolled patients in previous study had liver metastasis. The mPFS of the regorafenib in combination with chemotherapy group in this study was 3.94 months, and the mOS was 10.55 months; these figures are lower than those reported in another real-world study of regorafenib in combination with chemotherapy in China (13), which reported a mPFS of 2.2 months, and a mOS of 15.9 months. However, both studies were retrospective studies with a limited number of cases and a high number of biases. Thus, large-scale prospective studies need to be conducted to confirm the efficacy and safety of regorafenib combination chemotherapy. In addition, the prolonged mOS benefit in the regorafenib monotherapy group in this study may be related to the baseline selection of patients, which is one of the shortcomings of this study.

In this study, the univariate analysis suggested that the location of the primary foci, the degree of differentiation, and drug discontinuation significantly affected PFS, and the multivariate analysis suggested that the degree of differentiation (hyper differentiation) and drug discontinuation significantly affected PFS. The NLR was an independent factor affecting the OS of mCRC patients.

In addition, this study observed that in the real world, patients who remained on regorafenib-containing regimens after progression had a significantly better median PFS than those who discontinued regorafenib-containing regimens; however, no significant difference was found between the groups in terms of OS. This may be due to the limited duration of the follow-up period. This finding is consistent with the results reported by Jiang *et al.* (28). It further suggests that sustained anti-vascular therapy as a backline treatment could provide survival benefits for patients with advanced CRC, but further prospective studies are needed for validation.

In this study, 80.52% of the patients received a starting dose of 120 mg, 4% received a starting dose of 80 mg, and 15.58% received a starting dose of 160 mg. However, in relation to the final tolerated dose, while most patients still received a dose of 120 mg, the percentage of patients receiving a dose of 120 mg decreased to 63.63%, while the percentage of patients receiving a dose of 80 mg increased to 27.27%, and the percentage of patients receiving a dose of 160 mg decreased slightly to 9%. This also reflects real-world choices in clinical practice, where most patients receive a starting dose of 120 mg, which is then increased or decreased as appropriate according to the patient's tolerance level. REGOCC, a single-arm, prospective, phase-II clinical study in Japan (29), showed that a 120-mg starting dose of regorafenib, followed by an increase to 160 mg or a decrease to 80 mg, as tolerated by the patients, did not affect the survival benefit for the patients, and that the incidence of adverse reactions was consistent with the known safety profile. This study examined the relationship between the final tolerated dose and survival. The patients receiving 120 mg of regorafenib in this study had the most significant mOS benefit (17.41 months), which is also consistent with the findings of a previous retrospective study in China that explored the relationship between regorafenib dose and prognosis (28).

Regorafenib brings hope to patients with mCRC, but it is still important to pay close attention to the AEs it causes. A meta-analysis showed that the most common AEs of regorafenib treatment for mCRC were HSFRs (25–86%), hypertension (11–47%), and fatigue (2–73%) (30). In this study, HSFRs had the highest incidence (27.27%), followed by fatigue (19.48%), nausea (11.69%), fever (11.69%), hypertension (11.69%), cough (11.69%), and pain (11.69%), and the incidence of AEs $\geq$ 3 was 7.79%, which is basically in line with the above findings. Our study reported relatively good tolerability and safety. We also analyzed the relationship between HSFRs and patient prognosis. We found that patients who developed HSFRs had prolonged PFS and OS compared to those who did not develop HSFRs, which is also consistent with the findings of previous studies.

This study has limitations, first, the retrospective and non-randomized design of this study makes it subjective to potential biases in patient selection and interpretation of data, impacting the generalizability of the results. Furthermore, the small sample size (N=77) limits the statistical power and validity of the results. Prospective studies with large samples may provide more reliable indicators of the factors affecting OS in mCRC patients and provide references for clinical diagnosis and treatment.

Conclusions

Regorafenib is moderately efficacious and safe in the treatment of mCRC, and can be applied as a third-line therapy to improve OS. There are several options for combination regimens, considering the patient's baseline

condition and tolerance. Combination immunotherapy has the potential to provide a better survival benefit compared to regorafenib monotherapy, especially in patients with a low NLR ratio. However, this study was retrospective, the regimen of regorafenib was not standardized, decisions about the starting dose and dose adjustments during treatment lacked strict criteria, and some patients' information was missing, which affected the study's results to a certain extent. Prospective large-sample studies need to be conducted to further validate our results.

Acknowledgments

Funding: This project was funded by Tianjin Key Medical Discipline (Specialty) Construction Project (Grant No. TJYXZDXK-053B); Tianjin High-Level Personnel Training Program (TJSJMYXYC-D2-020).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-180/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-180/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-180/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-180/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Tianjin Union Medical Center (No. 2023B51), and the patients and/or their immediate family signed an informed consent form.

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Cite this article as: Yan H, Liu J, Zhang Y, Chen S, Xu J, Gao D, Li H, Fang X, Wang Y, Wang H, Wang H. Efficacy and safety of regorafenib in the treatment of metastatic colorectal cancer: a retrospective cohort study. J Gastrointest Oncol 2024;15(3):987-1001. doi: 10.21037/jgo-24-180

