Efficacy and safety of raltitrexed plus S-1 *versus* regorafenib in patients with refractory metastatic colorectal cancer: a real-world propensity score matching study

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Abstract

Background: Raltitrexed plus S-1 (RS) and regorafenib both showed considerable efficacy for metastatic colorectal cancer (mCRC) patients. This study aims to compare the effectiveness and safety of two different regimens in patients with refractory mCRC.

Methods: This retrospective cohort study included mCRC patients who were treated with RS or regorafenib from February 2017 to June 2021. A propensity score matching (PSM) analysis was conducted to balance the baseline characteristics of all patients. Progression-free survival (PFS), overall survival (OS), tumor response, and safety of two regimens were evaluated.

Results: A total of 187 patients were included in our study, with 107 patients in the RS group and 80 patients in the regorafenib group. After PSM, 78 pairs were recognized. Patients treated with RS had a semblable PFS compared to those treated with regorafenib before PSM (4.8 months *vs* 5.5 months, $p = 0.400$) and after PSM (4.7 months *vs* 5.4 months, $p = 0.430$). Patients in the RS group were associated with a longer OS than those in the regorafenib group (13.4 months *vs* 10.1 months, $p = 0.010$). A similar trend of OS was also obtained in the matched cohort (13.3 months *vs* 10.0 months, $p = 0.024$). Both objective response rate (12.8% *vs* 5.1%, $p = 0.093$) and disease control rate (53.8% *vs* 46.2%, $p = 0.337$) in the RS cohort were higher than those in the regorafenib group, without significant differences. Adverse events (AEs) of each group were well tolerated.

Conclusion: Patients treated with RS demonstrated a longer OS than those treated with regorafenib and had manageable AEs, which could be recognized as a primary choice for refractory mCRC.

Plain Language Summary

Efficacy and Safety of Raltitrexed plus S-1 *Versus* Regorafenib in Patients with Refractory Metastatic Colorectal Cancer: A Real-world Propensity Score Matching Study

Both raltitrexed plus S-1 (RS) and regorafenib showed considerable efficacy for metastatic colorectal cancer (mCRC) patients. No study has compared the two regimens yet. Therefore, we compare the efficacy and safety between RS and regorafenib to provide an optimal treatment option. We retrospectively included patients with mCRC who failed at least two standard treatments. All enrolled patients received RS or regorafenib treatments. We conducted a propensity score matching to eliminate differences in the enrolled patients. After the analysis, we found no significant differences in progression-free

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survival in patients between the two groups. However, patients treated with RS had a longer OS than those treated with regorafenib, whether before matching (13.4 months vs 10.1 months, p = 0.010) or after matching (13.3 months vs 10.0 months, p = 0.024). In addition, the adverse effects caused by cancer-related therapy were tolerable for the patient. Certainly, this is a non-randomized retrospective study with a small sample size, so we conducted a propensity score matching to minimize potential bias. Importantly, this is the first research comparing the two treatments, and we believe that the results of this article could present a primary choice for clinical doctors dealing with patients with standard treatments that failed mCRC.

Keywords: colorectal cancer, prognosis, raltitrexed, regorafenib, S-1

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Introduction

Colorectal cancer (CRC) is the third-most commonly diagnosed cancer worldwide and the fourth leading cause of cancer-related death globally.[1] As early diagnosis of colorectal cancer is complex and difficult, 25% of patients present with metastatic colorectal cancer (mCRC) when diagnosed,[2] with a poor 5-year survival of less than 15%. Standard treatments consisting of cytotoxic drugs (fluorouracil, irinotecan, and oxaliplatin) combined with targeted drugs (bevacizumab or cetuximab) can achieve a particular effect in the initial stage.[3] However, as the disease progresses, the effectiveness of existing treatments is limited. Therefore, effective drugs are not available at present, and further therapeutic regimens are required to improve the survival of mCRC.

Regorafenib was demonstrated to significantly improve the progression-free survival (PFS) and overall survival (OS) of patients with refractory mCRC in the CONCUR[4] and CORRECT[5] phase-III trials. And it was recommended as a standard posterior line treatment for patients with mCRC who have previously received fluorouracil, oxaliplatin, and irinotecan-based chemotherapy.[6] S-1, a fluorouracil derivative, could effectively hinder the growth and proliferation of new vascular endothelial cells in tumor tissue, thus inhibiting tumor. S-1 monotherapy or combination therapy has demonstrated a considerable benefit for CRC patients.[7,8] Raltitrexed, as a specific thymidylate synthase inhibitor, could inhibit the activity of the target enzyme of fluorouracil, thus demonstrating a synergistic effect with fluorouracil.[9] Our previous studies have demonstrated the effectiveness and safety of the combination of raltitrexed plus S-1 (RS) with or without bevacizumab in patients with refractory mCRC.[10,11] However, no studies have compared the RS and regorafenib. Herein, we aimed to make a comparison between RS and regorafenib in patients with mCRC who failed the previous standard treatment to explore the efficacy and safety of these two regimens.

Materials and methods

Study design and patients

This retrospective cohort study consecutively collected patients diagnosed with colorectal cancer who received RS or regorafenib after the failure of at least two standard treatments from February 2017 to June 2021 in our hospital. The reporting of this study conformed to the STROBE statement.[12] Patients would be included if they met the following criteria: (1) pathologically confirmed unresectable or metastatic colorectal adenocarcinoma with at least one measurable disease according to the Response Evaluation Criteria in Solid Tumors (v1.1);[13] (2) age was or older than 18 years; (3) previous standard therapy failed. Patients were excluded if they lack complete clinical materials; were combined with other targeted therapy; had undergone local treatment on measurable diseases before the initial evaluation; or were complicated with other serious physical illnesses. Notably, the crossover administration was also excluded in this study. The study was approved by the Institutional Review Board of West China Hospital, Sichuan University, Chengdu, China [Approval number: 2021 Review

(NO.1416)] on 10 November 2021. All the patients were collected from the database in West China Hospital, Sichuan University, and patients' details were hidden. Exemption of informed consent was granted by Institutional Review Board of West China Hospital, Sichuan University.

Endpoint's definition

OS was defined as the time between the onset of treatment and death by any cause. PFS was measured from the time starting the treatment to the date of disease progression or death of any cause. Objective response rate (ORR) was defined as a complete response (CR) or partial response (PR), while disease control rate (DCR) was defined as a CR, PR, or stable disease. The primary survival endpoint was OS, and the secondary endpoints were PFS, ORR, DCR, and safety. We performed the follow-up every 2 to 3 months. Most were followed up by telephone, and a few were followed up with the assistance of local departments of the census. Adverse events (AEs) were assessed in accordance with the Common Terminology Criteria for Adverse Events, version 4.03.

Propensity score matching

Propensity score matching (PSM) for the two groups was performed using a 1:1 ratio by R statistical programming language software version 4.1.1. To make the differences in patients' baseline characteristics minimal, we included the variables with potential effects on prognosis, including primary tumor location, RAS status, BRAF status, surgery, first-line therapy with target drugs, second-line therapy with target drugs, and therapy line in this propensity score model. Chi-square tests or Fisher exact tests were performed to assess the statistical significance of differences in covariates between treatment groups before and after matching. PSM of the two cohorts was then conducted with a caliper of 0.24 on the propensity scale.

Statistical analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, Armonk, NY) and *R* version 4.1.1. The Kaplan–Meier curves were used in performing the survival, including PFS and OS. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to compare the risk of the two regimens. *P*-value less than 0.05 in a two-tailed test was used to define statistical significance.

Results

Patients and baseline characteristics

A total of 187 patients meeting inclusion and exclusion criteria in West China hospital from February 2017 to June 2021 were collected, with 107 in the RS cohort and 80 in the regorafenib cohort. The flow chart for patient selection is shown in Figure 1. The baseline characteristics of patients treated with RS were generally similar to those treated with regorafenib (Table 1). Concretely, tumors in both groups were predominantly located on the left side, with mostly increased levels of CEA and CA199 before the treatment. Liver metastases were the most common metastatic lesions, occurring in about 70% of patients, followed by lung, lymph nodes, and bone metastases. A majority of patients were complicated by multiple metastases. Besides, RAS mutation, including KRAS and NRAS, appeared in 36.2–40.2% of the included population, while BRAF mutation occurred in 5.6% of patients in the RS group and 3.8% of patients in the regorafenib group, respectively. Poor pathological differentiation accounted for a small ratio in the RS group (23.4%) and the regorafenib group (18.8%). The proportion of patients in the T4 stage (55%) in the regorafenib group was higher than that in the RS group (41.1%). Nonetheless, the difference was not significant. As for the treatment, the majority of patients had previously undergone surgery. They received similar targeted therapies including anti-epidermal growth factor receptor and anti-vascular endothelial growth factor drugs (Supplementary Table 1). Importantly, RS or regorafenib was selected as the third-line therapy for most patients with mCRC, and only a small part of patients received it as their fourth or higher-line treatment. Most of them did not receive any subsequent therapy (Supplementary Table 2). After balancing the patients' baseline characteristics, 78 cases in each cohort were identified in the PSM (Figure 1). In the matched cohort, no significant differences were discovered between the RS and the regorafenib cohort in all variables (Table 1).

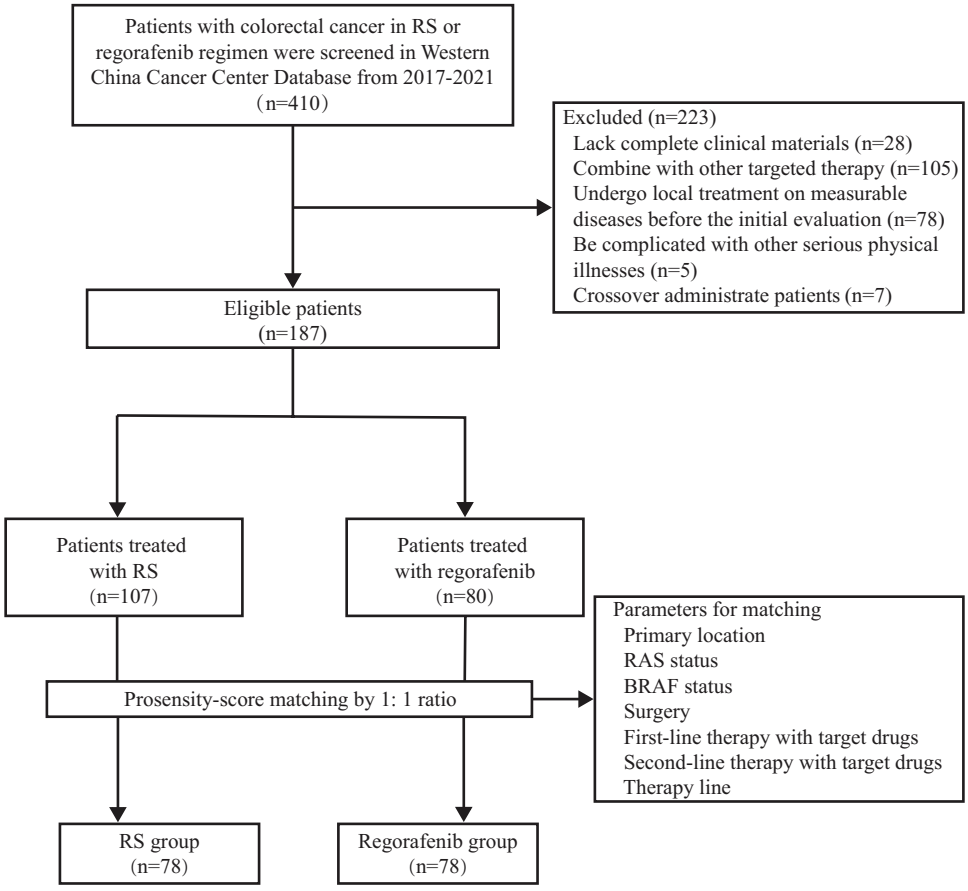

Figure 1. Flow diagram of patient selection.
RS, raltitrexed plus S-1.

Efficacy

The median follow-up period was 17.3 (14.2–20.6) months in the RS group and 11.5 (9.3–11.7) months in the regorafenib group. Before PSM, patients in the RS group had a comparable median PFS to those in the regorafenib group (4.8 months *vs* 5.5 months, $p = 0.40$). Nevertheless, patients in the RS group had a superior OS than those in the regorafenib group (13.4 months *vs* 10.1 months, $p = 0.01$). Similar prognostic trends for PFS and OS were observed in the matched cohort: patients treated with RS had a semblable PFS to those treated with regorafenib (4.7 months *vs* 5.4 months, $p = 0.43$). Patients in the RS cohort were associated with a longer median OS than those in the regorafenib cohort (13.3 months *vs* 10.0 months, $p = 0.02$; Figure 2).

The tumor response of all the patients before and after matching was summarized in Table 2. No patient had a CR in either group. Before PSM, 12.1% (13/107) patients achieved PR in the RS group, and 5.0% (4/80) patients obtained PR in the regorafenib group. No significant difference was found in ORR between the two groups ($p = 0.092$). In addition, patients in the RS group displayed a similar DCR compared with those in the regorafenib group (54.2% *vs* 45.0%, $p = 0.21$). After PSM, 12.8% (10/78) and 5.1% (4/78) patients showed PR in the RS and regorafenib groups, respectively. Both the ORR (12.8% *vs* 5.1%, $p = 0.093$) and the DCR (53.8% *vs* 46.2%, $p = 0.34$) in the RS group were quantitatively higher than those in the regorafenib group. However, the difference was not significant either in the unmatching cohort or the matching cohort.

Subgroup analysis

Furthermore, to better define prognostic differences between RS and regorafenib groups, we performed a subgroup analysis for PFS and OS in the matched cohort (Figure 3). No statistical differences were obtained between these two groups

Table 1. Baseline characteristics of all eligible patients.

Variables	Before matching		*p* value	After matching		*p* value
	RS, *n* = 107	Regorafenib, *n* = 80		RS, *n* = 78	Regorafenib, *n* = 78	
Age (%)			0.798			1.000
Age (<60)	59 (55.1)	42 (52.5)		41 (52.6)	40 (51.3)	
Age (⩾60)	48 (44.9)	38 (47.5)		37 (47.4)	38 (48.7)	
Sex (%)			0.834			1.000
Male	57 (53.3)	45 (56.3)		43 (55.1)	44 (56.4)	
Female	50 (46.7)	35 (43.8)		35 (44.9)	34 (43.6)	
Primary location (%)			0.946			1.000
Left side	84 (78.5)	64 (80.0)		63 (80.8)	62 (79.5)	
Right side	23 (21.5)	16 (20.0)		15 (19.2)	16 (20.5)	
CEA (%)			0.125			0.139
Normal level	7 (6.5)	7 (8.8)		5 (6.4)	7 (9.0)	
1–10 times of normal level	35 (32.7)	20 (25.0)		25 (32.1)	20 (25.6)	
⩾10 times of normal level	63 (58.9)	46 (57.5)		47 (60.3)	44 (56.4)	
Unknown	2 (1.9)	7 (8.8)		1 (1.3)	7 (9.0)	
CA199 (%)			0.566			0.439
Normal level	29 (27.1)	17 (21.2)		23 (29.5)	17 (21.8)	
1–10 times of normal level	35 (32.7)	29 (36.2)		30 (38.5)	29 (37.2)	
⩾10 times of normal level	38 (35.5)	27 (33.8)		22 (28.2)	25 (32.1)	
Unknown	5 (4.7)	7 (8.8)		3 (3.8)	7 (9.0)	
Liver metastasis (%)			0.268			0.485
No	27 (25.2)	27 (33.8)		21 (26.9)	26 (33.3)	
Yes	80 (74.8)	53 (66.3)		57 (73.1)	52 (66.7)	
Lung metastasis (%)			0.190			0.200
No	57 (53.3)	34 (42.5)		43 (55.1)	34 (43.6)	
Yes	50 (46.7)	46 (57.5)		35 (44.9)	44 (56.4)	
Lymph node metastasis (%)			0.491			0.282
No	77 (72.0)	62 (77.5)		53 (67.9)	60 (76.9)	
Yes	30 (28.0)	18 (22.5)		25 (32.1)	18 (23.1)	
Bone metastasis (%)			0.689			0.401
No	98 (91.6)	71 (88.8)		73 (93.6)	69 (88.5)	

(Continued)

Table 1. (Continued)

Variables	Before matching		*p* value	After matching		*p* value
	RS, *n* = 107	Regorafenib, *n* = 80		RS, *n* = 78	Regorafenib, *n* = 78	
Yes	9 (8.4)	9 (11.3)		5 (6.4)	9 (11.5)	
Other metastases (%)			0.442			0.716
No	75 (70.1)	61 (76.3)		56 (71.8)	59 (75.6)	
Yes	32 (29.9)	19 (23.8)		22 (28.2)	19 (24.4)	
Number of metastases (%)			0.700			0.870
Single metastasis	40 (37.4)	33 (41.3)		30 (38.5)	32 (41.0)	
Multiple metastases	67 (62.6)	47 (58.8)		48 (61.5)	46 (59.0)	
RAS status (%)			0.793			0.803
Wild	59 (55.1)	48 (60.0)		42 (53.8)	46 (59.0)	
Mutation	43 (40.2)	29 (36.2)		33 (42.3)	29 (37.2)	
unknown	5 (4.7)	3 (3.8)		3 (3.8)	3 (3.8)	
BRAF status (%)			0.832			0.928
Wild	98 (91.6)	75 (93.8)		72 (92.3)	73 (93.6)	
Mutation	6 (5.6)	3 (3.8)		4 (5.1)	3 (3.8)	
unknown	3 (2.8)	2 (2.5)		2 (2.6)	2 (2.6)	
Differentiation degree (%)			0.222			0.211
Low	25 (23.4)	15 (18.8)		47 (60.3)	37 (47.4)	
High or mild	58 (54.2)	38 (47.5)		17 (21.8)	26 (33.3)	
Unknown	24 (22.4)	27 (33.8)		14 (17.9)	15 (19.2)	
T stage (%)			0.101			0.126
3	45 (42.1)	22 (27.5)		33 (42.3)	21 (26.9)	
4	44 (41.1)	44 (55.0)		33 (42.3)	43 (55.1)	
Unknown	18 (16.8)	14 (17.5)		12 (15.4)	14 (17.9)	
N stage (%)			0.119			0.222
Negative	18 (16.8)	6 (7.5)		13 (16.7)	6 (7.7)	
Positive	70 (65.4)	62 (77.5)		53 (67.9)	60 (76.9)	
Unknown	19 (17.8)	12 (15.0)		12 (15.4)	12 (15.4)	
Surgery (%)			0.142			0.460
No	21 (19.6)	24 (30.0)		17 (21.8)	22 (28.2)	
Yes	86 (80.4)	56 (70.0)		61 (78.2)	56 (71.8)	

(Continued)

Table 1. (Continued)

Variables	Before matching		*p* value	After matching		*p* value
	RS, *n* = 107	Regorafenib, *n* = 80		RS, *n* = 78	Regorafenib, *n* = 78	
First-line regimen (%)			0.374			0.218
Oxaliplatin-based therapy[a]	81 (75.7)	62 (77.5)		60 (76.9)	61 (78.2)	
Irinotecan-based therapy[b]	24 (22.4)	14 (17.5)		18 (23.1)	14 (17.9)	
Other	2 (1.9)	4 (5.0)		0 (0.0)	3 (3.8)	
Second-line regimen (%)			0.700			0.821
Oxaliplatin-based therapy	22 (20.6)	13 (16.2)		16 (20.5)	13 (16.7)	
Irinotecan-based therapy	73 (68.2)	56 (70.0)		52 (66.7)	55 (70.5)	
Other	12 (11.2)	11 (13.8)		10 (12.8)	10 (12.8)	
Combination with target therapy in first-line treatment (%)			0.535			0.735
No	74 (69.2)	51 (63.7)		53 (67.9)	50 (64.1)	
Yes	33 (30.8)	29 (36.3)		25 (32.1)	28 (35.9)	
Combination with target therapy in second-line treatment (%)			0.390			0.744
No	48 (44.9)	30 (37.5)		33 (42.3)	29 (38.5)	
Yes	59 (55.1)	50 (62.5)		45 (57.7)	49 (61.5)	
Therapy line (%)			0.605			1.000
3	81 (75.7)	57 (71.2)		56 (71.8)	55 (70.5)	
>3	26 (24.3)	23 (28.8)		22 (28.2)	23 (29.5)	

RS, raltitrexed plus S-1.
[a]Treatment regimen which includes oxaliplatin, such as FOLFOX, XELOX, and CAPOX.
[b]Treatment regimen which includes irinotecan, such as XELIRI and FOLFIRI.

in PFS for nearly all parameters analyzed. As for OS, patients in the RS group had a superior prognosis with following beneficial factor, including younger age (<60 years old), higher CEA levels at baseline (>10 times of normal level), absence of lung metastasis, mutated RAS gene, wild BRAF gene, low pathological differentiation, lymph node invasion, and combination with target therapy in the first- or second-line treatment.

Adverse events

AEs in all patients were summarized in Table 3. In this study, nearly all patients underwent AEs caused by cancer-related therapy. Generally, it was universal for AEs in the RS cohort than that in the regorafenib group. The hematological AEs were quite common in the RS group, including anemia (45%), leucopenia (40%), AST/ALT increased (40%), neutropenia (38%), as well as thrombocytopenia (24%). Some unexceptional AEs during the tumor therapy, like fatigue (59%), anorexia (35%), vomit (30%), and diarrhea (22%), also occurred. Notably, hyperpigmentation happened to 46% population in the RS cohort while hand–foot skin reaction only happened to 19%. On the contrary, no hyperpigmentation was observed in the regorafenib group, while hand–foot skin reaction (69%) was the most common AE. The secondary common AEs were hyperbilirubinemia

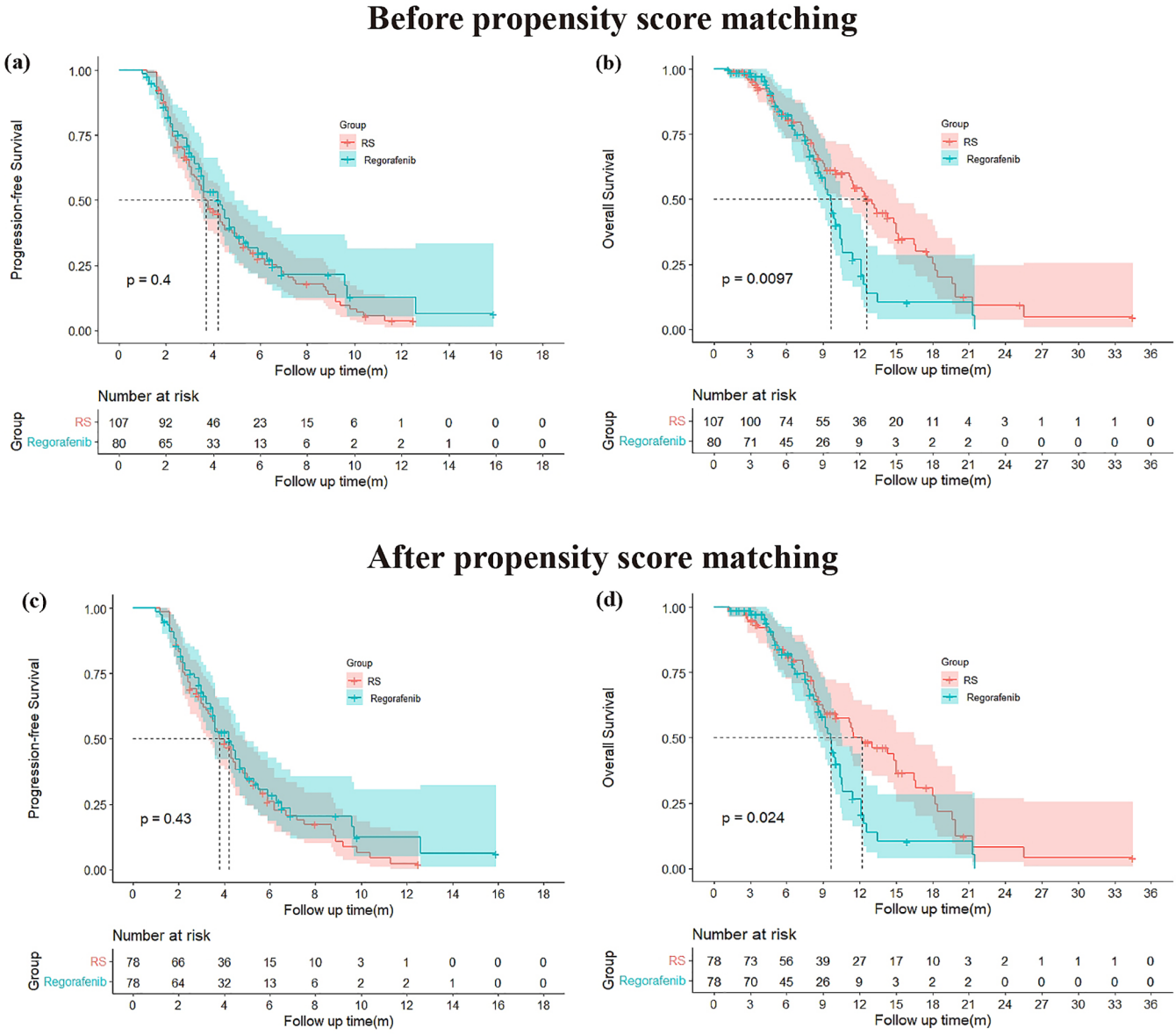

Figure 2. Kaplan–Meier survival curves for patients before matching and after matching: (a) progression-free survival of patients before matching, (b) overall survival of patients before matching, (c) progression-free survival of patients in the matched cohort, and (d) overall survival of patients in the matched cohort.
RS, raltitrexed plus S-1.

(37%), followed by AST/ALT increased (27%), vomit (26%), hypertension (24%), anorexia (20%), and so on. It was worthy to note that the incidence of grade ⩾ 3 hand–foot skin reaction and hypertension in the regorafenib group could reach 15% and 10%, respectively.

Discussion

Our previous phase-II trial[10,11] suggested that RS with or without bevacizumab was a promising third- or later-line treatment option in patients with refractory mCRC. Regorafenib has been approved worldwide as a recommended drug for the third-line therapy of mCRC.[6,14] Criteria for the appropriate selection of RS or regorafenib have not yet been established. Thus, we explored retrospectively the efficacy and toxicity of RS *versus* regorafenib in mCRC patients who were intolerant to standard therapies. This study, for the first time, concluded that in patients with standard treatments who failed mCRC, the RS has an

Table 2. The overall response of all the patients before and after matching.

Best response	Before matching			After matching		
	RS, $n = 107$	Regorafenib, $n = 80$	p value	RS, $n = 78$	Regorafenib, $n = 78$	p value
PR	13 (12.1%)	4 (5.0%)		10 (12.8%)	4 (5.1%)	
SD	45 (42.1%)	32 (40.0%)		32 (41.0%)	32 (41.0%)	
PD	49 (45.8%)	44 (55.0%)		36 (46.2%)	42 (53.8%)	
ORR	13 (12.1%)	4 (5.0%)	0.092	10 (12.8%)	4 (5.1%)	0.093
DCR	58 (54.2%)	36 (45.0%)	0.213	42 (53.8%)	36 (46.2%)	0.337

DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; RS, raltitrexed plus S-1; SD, stable disease.

OS advantage over regorafenib despite its obvious but controllable AEs. Although no statistical difference was obtained, ORR in the RS group was twice as high as that in the regorafenib group. In terms of PFS and DCR, these two regimens are comparable.

In this study, the PFS and OS of regorafenib were 5.4 and 10.0 months, respectively, which are longer than those in the CONCUR[4] (3.2 and 8.8 months) and CORRECT[5] (1.9 and 6.4 months) trials. Nonetheless, the DCR in this study (46.2%) was comparable to that in the CONCUR (51.0%) and CORRECT (41.0%) trials. A relatively higher proportion of the third-line treatments and a longer efficacy evaluation and patients' follow-up period in this study may contribute to the above outcomes. Our study indicated a similar DCR (53.8%) in the RS group to that in the previous study (54.3%).[10] But the PFS (4.7 months) and OS (13.3 months) of RS in this study are a little longer than those in that study with 3.6 and 12.4 months, respectively. The likely reason is that the proportion of patients treated with targeted therapies, either cetuximab or bevacizumab, in this study (about 60%) was higher than that in that study (49.9%). Although, previous studies suggested that the effect of regorafenib might be affected by previous treatments.[4] Some studies proved that trifluridine/tipiracil (TAS-102) was an effective treatment option for refractory colorectal cancer,[15,16] while combination with bevacizumab would make survival benefit more prominent.[17–19] The PFS time was similar to that in our study. However, we did not explore the effects of combination therapy in this research, and more studies are needed in the future. The therapy lines in the two groups are well balanced in the current research (Table 1). Crossover administration is excluded in this study, and the proportion of posterior line treatment is also semblable between the two groups, making the outcomes more credible.

Up to now, the subgroups of patients who can benefit from RS or regorafenib remain unclear, and the prognostic factor of these two regimens is not very pronounced. Previous researches indicated that the density reduction in lung metastases,[20] a good Eastern Cooperative Oncology Group performance status, a long history of metastatic disease ($\geqslant$18 months), and the presence of a limited lung metastatic disease are associated with better prognosis.[21] Some studies also pointed out that Cancer-Inflammation Prognostic Index has an excellent discriminatory power in predicting mortality for patients treated with regorafenib.[22] As for the prognostic predictors of the RS regimen, there have not been reported because of its inprevalence in mCRC. In our study, the following characteristics like old age (year $>$ 60), less than 10 times CEA levels at baseline, lung metastasis, wild RAS, higher differentiation, without target therapy in the first- or second-line treatment, and lymph node negative seems to be associated with a better prognosis for regorafenib, because patients with the above factors in the regorafenib group had a similar OS to those in the RS group.

As for AEs, we concluded that RS was associated with higher toxicity than regorafenib overall. RS was generally well tolerated, and the common toxicities observed in our study resembled those

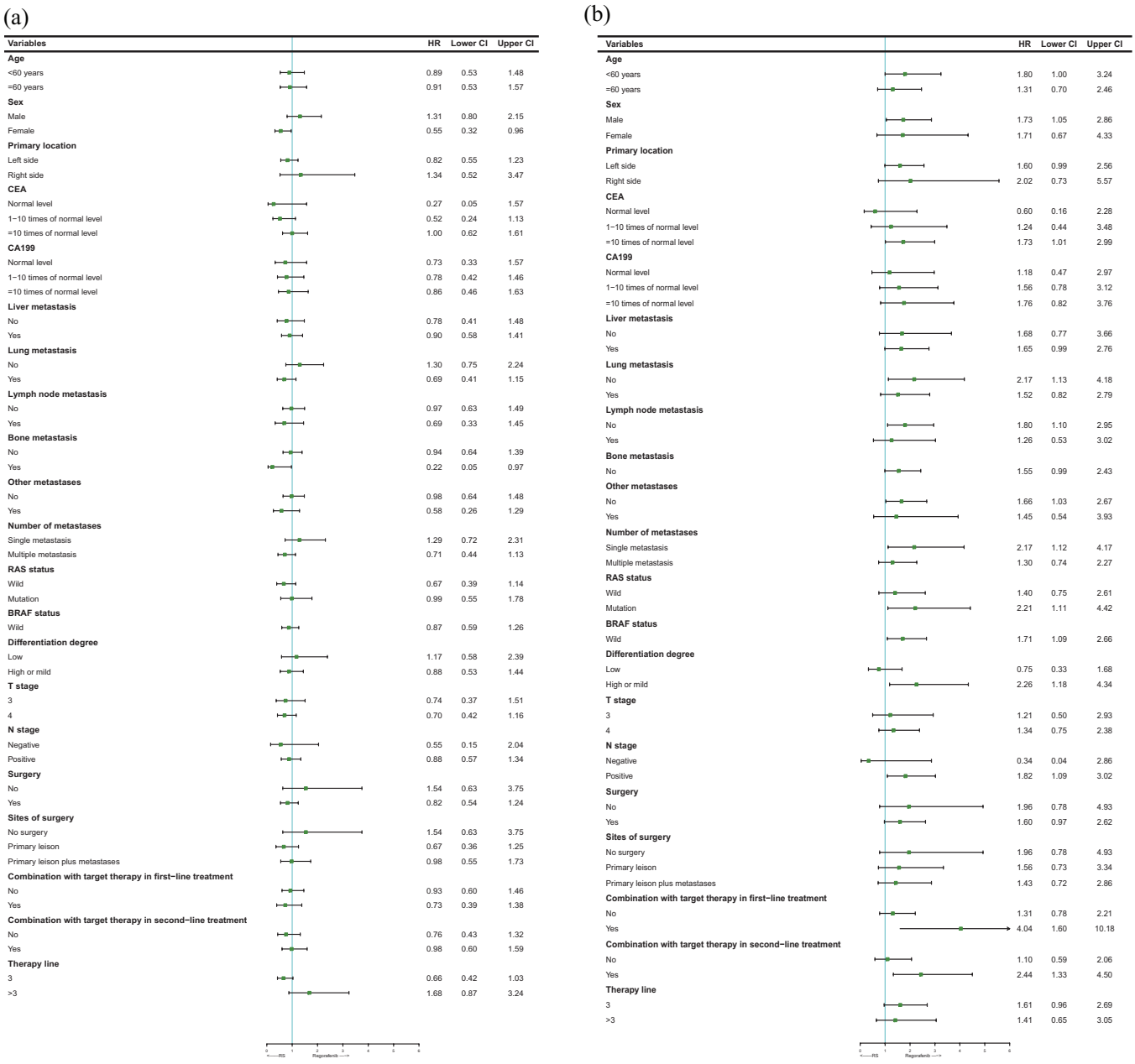

Figure 3. Subgroup analyses for progression-free survival and overall survival: (a) progression-free survival and (b) overall survival. RS, raltitrexed plus S-1.

reported in our published study.[10] In the RS group, the most common AEs were fatigue, bone marrow depression, liver dysfunction, and hyperpigmentation. The neutropenia (8%), leucopenia (7%), thrombocytopenia (6%), anorexia (6%), and fatigue (6%) were the most common grade 3/4 toxicities.

The AEs of regorafenib reported here are consistent with those reported in other clinical trials.[5,23,24] In the regorafenib group, the most common grade 3/4 toxicities were hand–foot skin reaction (15%), hypertension (10%), and hyperbilirubinemia (6%), which were significantly higher than those in the RS group. However, the incidences of bone marrow depression and gastrointestinal AEs in the regorafenib group were lower than that in the RS group. As a result, the early and proactive prophylaxis, and management of AEs, especially neutropenia, leucopenia,

Table 3. Adverse events of all the included patients.

	RS		Regorafenib	
	(*n* = 107)		(*n* = 80)	
	All grade (%)	Grade ⩾ 3 (%)	All grade (%)	Grade ⩾ 3 (%)
All events	99	58	98	53
Leucopenia	40	7	17	3
Neutropenia	38	8	10	2
Anemia	45	5	14	3
Thrombocytopenia	24	6	11	3
Diarrhea	22	6	19	2
Vomit	30	4	26	0
Anorexia	35	6	20	2
Fatigue	59	6	15	1
AST/ALT increased	40	5	27	7
Hyperbilirubinemia	10	1	37	6
Hand–foot skin reaction	19	4	69	15
Rash	15	3	10	1
Hyperpigmentation	46	1	0	0
Proteinuria	14	2	13	2
Hypertension	4	1	24	10

RS, raltitrexed plus S-1.

thrombocytopenia, liver function test abnormalities, hand–foot skin reaction, and hypertension, which were the most common AEs needing therapeutic intervention, are essential to ensure patients can keep on therapy.

The study had the following limitations that should be considered: first, this was a non-randomized retrospective research with a small sample size, and the treatment regimen was chosen by different researchers, which resulted in potential selection bias. Therefore, we conducted PSM analysis between the RS and the regorafenib group. Second, patients' quality of life, one of the crucial factors in salvage-line setting, could not be evaluated. Third, all the enrolled patients in our study were Chinese. Nevertheless, there were no ethnic differences in previous phase-III trials on the safety and efficacy of RS and regorafenib; therefore, our outcomes may be applied to the majority regardless of ethnicity. Further prospective clinical trials in larger cohorts are warranted to validate this study results.

Conclusion

Our study suggests that RS therapy is associated with a longer OS, with manageable toxicities, compared with regorafenib as the primary treatment choice in patients with standard treatments who failed mCRC.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was approved by the Institutional Review Board of West China Hospital, Sichuan University, Chengdu, China

[(Approval number: 2021 Review (NO.1416)] on 10 November 2021. Patients' details were hidden. Exemption of informed consent was granted by Institutional Review Board of West China Hospital, Sichuan University.

Consent for publication

Not applicable

Author contribution(s)

Yu-Wen Zhou: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft.

Jia-Ling Wang: Formal analysis; Methodology; Software; Writing – original draft.

Qing-Fang Li: Formal analysis; Investigation; Software; Writing – original draft.

Yuan-Lin He: Data curation; Methodology; Writing – original draft.

Lin-Juan Li: Data curation; Investigation; Resources.

Rui-Zhi Liu: Investigation; Methodology; Project administration; Resources.

Ye Chen: Resources; Supervision; Validation.

Shuang Zhang: Investigation; Resources; Validation.

Meng Qiu: Conceptualization; Supervision; Validation; Writing – review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data analyzed in this study are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

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