Cancer Management and Research

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ORIGINAL RESEARCH

Real-World Results of Raltitrexed Combined with S-1 and Bevacizumab in Heavily Pretreated Metastatic Colorectal Cancer

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Purpose: Treatment options for refractory metastatic colorectal cancer (CRC) are scarce. This retrospective study aimed to evaluate the efficacy and safety of raltitrexed combined with S-1 and bevacizumab in patients with heavily pretreated metastatic CRC in a clinical real-world setting.

Patients and Methods: Records of patients with metastatic CRC refractory to standard therapies who initiated raltitrexed plus S-1 and bevacizumab from October 2017 to December 2021 were retrospectively reviewed at our institution. The study endpoints included median overall survival (OS), overall response rate (ORR), progression-free survival (PFS), disease control rate (DCR), and adverse events (AEs).

Results: Forty-four patients with metastatic CRC, who had previously undergone standard chemotherapy received the regimen comprising raltitrexed plus S-1 and bevacizumab. As of March 2022, the median follow-up was 23.2 months (95% confidence interval 15.8−30.6). The median OS and median PFS were 13.5 (95% CI 9.9–17.1) and 4.7 months (95% CI 3.6–5.8), respectively, with a 16-week PFS rate of 60.9%. Among 43 patients with measurable lesions, the ORR and DCR were 7.0% (3/43) and 65.1% (28/43), respectively. Patients without peritoneal metastases (P = 0.003, hazard ratio 0.160, 95% CI 0.048−0.531), lower carcinoembryonic antigen level (≤42.8 ng/mL) (P = 0.039, HR 0.382, 95% CI 0.153−0.952), and no previous treatment with both vascular endothelial growth factor inhibitors (VEGF) and S-1 (P = 0.020, HR 0.215, 95% CI 0.059−0.785) had better OS. The incidence of any grade of treatment-related AEs was 88.6%, most of which were mild to moderate, and no treatment-related deaths occurred.

Conclusion: Raltitrexed combined with S-1 and bevacizumab shows promising antitumor activity and safety and could be an alternative for patients with metastatic CRC who are refractory or intolerant to standard therapy.

Keywords: refractory metastatic colorectal cancer, chemotherapy, target therapy, angiogenesis

Introduction

Colorectal cancer (CRC) is one of the most common causes of cancer mortality worldwide; approximately 19.3 million new cases diagnosed, and over 9,958,133 deaths recorded globally in 2020.[1] The heavy burden of the disease with a poor five-year overall survival (OS, 5–38%) poses a greater global challenge.[2,3] Therefore, it is crucial to explore more treatment strategies to improve the OS of patients with metastatic CRC. Currently, microsatellite instability status (MSI-H or MSI-L/MSS) or mismatch repair protein phenotype (dMMR or pMMR) are important predictive biomarkers that guide therapies. The NCCN and CSCO clinical guidelines recommend immunotherapy as a standard treatment for all dMMR/MSI-H mCRC.[4,5] For most patients with low microsatellite instability, microsatellite stability or proficient mismatch repair (MSI-L/MSS/pMMR), fluoropyrimidine, irinotecan, and oxaliplatin—with or without targeted therapies, including bevacizumab or cetuximab (only for *RAS* wild type)—are the mainstay treatments. One of third-line treatment strategies is the reintroduction

Received: 21 November 2022
Accepted: 14 March 2023
Published: 20 March 2023

of first-line chemotherapy. However, retrospective small-sample studies have demonstrated that the reintroduction of first-line chemotherapy exert very limited efficacy and that adverse events, such as hand-foot skin reactions and peripheral neurotoxicity, may recur or accumulate.[6] Other drugs can be used after second line including Regorafenib, fruquintinib, and TAS102, all of which are orally administration. Regorafenib is a multikinase inhibitor, fruquintinib is a small-molecule inhibitor of VEGFR receptors 1, 2 and 3 while TAS-102 is a fluoropyrimidine. Regorafenib, fruquintinib, and TAS102 demonstrated superior efficacy than placebo in several Phase III clinical studies, with PFS and OS ranging from 2−3 months and 7−9 months, respectively; however, these therapies are expensive.[7–11] Phase II trials suggested that the DCR of TAS102 combined with bevacizumab was approximately 60%; PFS was 4−6 months, which was double that of TAS102 monotherapy, and OS was more than 10 months.[12–14] However, these results are not yet supported by Phase III clinical studies (the Phase III SUNLIGHT trial is still ongoing [NCT04737187]).[15] Furthermore, rechallenging with cetuximab only benefited patients harboring RAS wild type in circulating DNA in the plasma.[16] Results of an early-stage study of anti-angiogenesis tyrosine kinases inhibitor (TKI) combined with programmed death-1 (PD-1) antibody showed inconsistent outcomes.[17–27] The ORR fluctuates between 36% and 0%, and the DCR fluctuates between 80% and 40%. PFS ranging from less than 2 months to more than 7 months and OS of 7–11 months cannot be mutually replicated or verified among different studies. Thus, there remains an unmet clinical need for treatment for standard therapy-resistant metastatic CRC.

Raltitrexed, an antimetabolite folate analog transported into cells by the carrier of reduced folic acid and converted into polyglutamate by folic acid polyglutamate synthase, has a place in the first- or second-line settings recommended by clinical guidelines worldwide owing to its promising efficacy and safety compared to fluorouracil. Notable, Raltitrexed that acts on the folate-binding site of thymidylate synthase (TS enzyme) and does not depend on dihydropyrimidine dehydrogenase (DPD enzyme) metabolism, is differed from 5FU which is converted into deoxyuracil nucleotides and binds to the pyrimidine-binding site of TS enzymes after entering cells in pharmacological mechanism. It is possible that, at least theoretically, Raltitrexed combined with 5FU or a fluorouracil derivative to pursue higher activity. Preclinical studies have suggested that raltitrexed and 5-FU have an incompletely overlapping spectrum of antitumor activity.[28–30] We inferred that raltitrexed combined with S-1, another fluorouracil derivative composed of 5FU prodrug tegafur, DPD enzyme inhibitor gimeracil, and oteracil potassium, can also enhance benefit, and can be even more when plus bevacizumab which have strongly demonstrated by clinical trials that can be reintroduced in the treatment of mCRC. Additionally, Phase II trials showed that S-1 monotherapy or combined therapy with bevacizumab achieved an ORR of 7−14.3%, DCR of 65−67.9%, PFS of 3.7−5.3 months, and OS of 8.6−9.9 months in metastatic CRC for which standard treatments failed.[31–33]

Given the limited treatment options in 2017, we applied raltitrexed plus S-1 and bevacizumab in clinical practice for heavily pretreated patients with metastatic CRC who had almost no other considerable treatment options. This study aimed to evaluate the efficacy and safety of raltitrexed plus S-1 and bevacizumab in a real-world setting.

Methods

Study Design and Patients

This was a single-center, retrospective, longitudinal cohort study of patients with metastatic CRC treated with raltitrexed plus S-1 and bevacizumab from October 2017 to December 2021 at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College. Patient follow-up was performed until March 2022. Patients were included in this study based on the following criteria: histologically confirmed adenocarcinoma located in the colon or rectum with metastatic disease-resistant features or intolerance to standard treatments, including fluoropyrimidine (fluorouracil and capecitabine), irinotecan, and oxaliplatin with or without raltitrexed, S-1, and targeted therapies (cetuximab or bevacizumab, regorafenib, fruquintinib) or in whom the consideration of standard treatment options was not available or feasible; at least 18 years of age; measurable and/or accessible lesions in accordance with Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria; pretreatment with raltitrexed plus S-1 and bevacizumab for metastatic CRC for at least 1 cycle; and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.

The treatment regimen consisted of an intravenous infusion of raltitrexed (4 mg/m^2) and bevacizumab (7.5 mg/kg) on day 1 every 21 days. S-1 (40−60 mg) was orally administered twice a day for 14 days according to body surface area

(dosage for body surface area <1.25 m^2, 40 mg bid; ≥1.25–<1.5 m^2, 50 mg bid; ≥1.5 m^2, 60 mg bid) followed by 1 week off.

The following baseline clinical characteristics were recorded for each patient: age, sex, ECOG performance status, primary cancer site, history of primary resection, sites of metastases, number of metastatic organs, time from first-line chemotherapy start, time from prior angiogenesis inhibitors, time from treatment start, *RAS* status (*KRAS* exons 2, 3, and 4, and *NRAS* exons 2, 3, and 4), $BRAF^{V600E}$ mutation status, microsatellite stability status (if available), and prior systemic therapies recorded in our medical record system.

Outcomes and Statistical Analysis

The study endpoints included OS, defined as the time from study treatment start to death from any cause; PFS, defined as the time from study treatment initiation to disease progression or death from any cause, whichever occurred first; overall response rate, defined as the proportion of patients with a complete response (CR) and partial response (PR) to study treatment; DCR, defined as the proportion of patients with a CR and PR plus stable disease lasting more than 6 weeks from study treatment start. Tumor response was evaluated by investigators every two cycles according to the RECIST 1.1 criteria. AEs were graded in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0.

Patient characteristics and treatment data are reported as frequencies and percentages for categorical variables. For continuous variables, median OS and PFS were generated using the Kaplan–Meier method. The Log rank test was performed for subgroup comparisons and a median with a 95% CI and range. The subgroups were based on sex, age, ECOG performance status, primary tumor location, sites and number of metastatic organs, *RAS* and $BRAF^{V600E}$ mutation status, treatment duration, number of prior systemic regimens for metastatic disease, time from first-line chemotherapy start, time from prior VEGF inhibitors start, time from prior fluoropyrimidine, prior systemic antitumor treatment, baseline carcinoembryonic antigen (CEA) level, and lymphocyte/monocyte ratio (LMR). We created Cox regression models using 17 dependent and 6 independent variables to evaluate hazard ratios (HRs) for the same subgroups. *P*-values <0.05 (two-sided) were considered statistically significant. Multivariate Cox analysis for OS was employed using forward stepwise regression, including primary location, peritoneum metastases, $BRAF^{V600E}$ status, treatment duration, history of VEGF inhibitors and S-1, and CEA level. Multivariate Cox analysis for PFS was based on treatment duration, history of VEGF inhibitors and S-1, and LMR. All statistical analyses were performed using SPSS 22.0 software (IBM, Armonk, NY, USA).

Results

Patients

Forty-four eligible patients were included in this study. Patient demographics and baseline characteristics are shown in Table 1. All patients had previously received fluoropyrimidine, oxaliplatin, and irinotecan. The median number of previous lines of treatment for metastatic CRC was 3 (range, 1−6), with 12 (27.3%) patients who received more than three lines of therapy and 21 (47.7%) patients who progressed to treatments comprising fluoropyrimidine. Further, 10 (22.7%), 10 (22.7%), and 4 (9.1%) patients were previously treated with raltitrexed, S-1, or both, respectively. Another 32 (72.7%) patients had previously received VEGF inhibitors (bevacizumab, n = 30; regorafenib, n = 7; fruiquintinib, n = 10; apatinib, n = 1; anlotinib, n = 1), and 13 (29.5%) patients previously received anti-epidermal growth factor receptor (EGFR) antibodies. Patients with *RAS*-mutant tumors accounted for approximately 59.1% of the cohort, and 4.5% of patients harbored $BRAF^{V600E}$ mutation. No patient had tumors with high microsatellite instability.

After study treatment discontinuation, 25 (56.8%) patients received subsequent antitumor therapies, including targeted drugs (regorafenib, fruquintinib, pyrotinib, apatinib, bevacizumab, or cetuximab) with or without cytotoxic chemotherapy and/or PD-1 antibodies.

Table 1 Patient Demographics

Characteristics	N (%)
Sex	
Male	25 (56.8)
Female	19 (43.2)
Age	
Median (range)	54 (44–72)
<60 years	26 (59.1)
≥60 years	18 (40.9)
ECOG	
0–1	41 (93.2)
2	3 (6.8)
Primary tumor site[†]	
Left	32 (72.7)
Right	11 (25)
Left and right	1 (2.3)
Primary tumor resection	
Yes	31 (70.5)
No	13 (29.5)
Disease stage at first diagnosis	
II	2 (4.5)
III	6 (13.6)
IV	34 (77.3)
NA	2 (4.5)
Time to metastasis	
Simultaneous	34 (77.3)
Metachronous	8 (18.2)
NA	2 (4.5)
Metastasis organ	
Liver	37 (84.1)
Lung	29 (65.9)
Peritoneum	6 (13.6)
Lymph nodes	21 (47.7)
Other metastases	17 (38.6)

(*Continued*)

Table 1 (Continued).

Characteristics	N (%)
Numbers of metastatic organs	
1	3 (6.8)
2	20 (45.5)
3	15 (34.1)
4	5 (11.4)
5	1 (2.3)
KRAS/NRAS mutational status	
Wildtype	15 (34.1)
Mutant	26 (59.1)
Unknown	3 (6.8)
$BRAF^{V600E}$ mutational status	
Wild type	39 (88.6)
Mutant	2 (4.5)
Unknown	3 (6.8)
MMR/MSI status	
pMMR/MSS/MSI-L	25 (56.8)
dMMR/MSI-H	0
Unknown	19 (43.2)
Prior systemic antitumor treatment	
VEGF inhibitors	32 (72.7)
Anti-EGFR antibodies	13 (29.5)
S-1	10 (22.7)
Raltitrexed	10 (22.7)
VEGF inhibitors and S-1‡	7 (15.9)
Number of prior systemic regimens for metastatic disease	
1	5‡ (11.4)
2	16 (36.4)
3	11 (25)
4	7 (15.9)
5	4 (9.1)
6	1 (2.3)

(*Continued*)

Table 1 (Continued).

Characteristics	N (%)
Time from first-line chemotherapy	
≥18 months	21 (47.7)
<18 months	23 (52.3)
Time from prior VEGF inhibitors	
≤1 month	27 (61.4)
>1 month	17 (38.6)
Time from prior fluoropyrimidine	
≤1 month	21 (47.7)
>1 month	23 (52.3)
LMR	
Median (range)	2.27(1.23–9.05)
LMR≤2.27	12 (27.3)
LMR>2.27	30 (68.2)
Unknown	2 (4.5)

Notes: [†]Left-sided tumors were defined as those in the colon splenic flexure, descending colon, sigmoid colon, rectosigmoid junction colon, or rectum. Right-sided tumors were defined as those in the cecum, ascending colon, transverse colon, or hepatic flexure of the colon. VEGF inhibitors included bevacizumab, regorafenib, fruiquintinib, apatinib, and anlotinib. [‡]VEGF inhibitors and S-1 were used separately early or late in previous treatments or as a combination regimen.

Abbreviations: EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; MSS, microsatellite stability; MSI-H, high microsatellite instability; MSI-L, low microsatellite instability; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair; NA, not available; LMR, lymphocyte/monocyte ratio.

Efficacy

The median follow-up time was 23.2 months (95% CI 15.84−30.56). Currently, three patients are still on the study treatment. The disease progressed in 41 patients, 30 of whom died. The median OS was 13.5 months (95% CI 9.9–17.1) (Figure 1), and the 6-month and 1-year OS rates were 82.4% and 57.5%, respectively.

Subgroup analysis showed an OS benefit for left-sided primary lesions, no peritoneum metastases, $BRAF^{V600E}$ wild type, treatment duration greater than three cycles, no previous treatment with VEGF inhibitors and S-1 (Figure 2), and CEA level ≤42.8 ng/mL. In the multivariate analysis, peritoneum metastases, previous treatment with both VEGF inhibitors and S-1 (used separately early or late), and CEA level >42.8 ng/mL were independent poor prognostic factors (Table 2).

The median OS of patients who received subsequent antitumor therapies was 16.9 months (95% CI 10.21−23.59). The median PFS was 4.7 months (95% CI 3.6–5.8) (Figure 3). PFS at 16 weeks was 60.9%. Subgroup analysis showed a PFS benefit for patients with treatment duration greater than three cycles, LMR > 2.27, and without previous treatment of VEGF inhibitors and S-1 (used separately early or late). In multivariate analysis, LMR > 2.27 (P = 0.010, HR 0.366, 95% CI 0.170−0.388) and no previous VEGF inhibitors and S-1 treatment (used separately early or late) (P = 0.005, HR 0.271, 95% CI 0.108−0.678) were significantly associated with PFS. Among 43 patients with measurable lesions, none had complete response, three had partial response and 25 had stable disease, resulting in a 7% ORR and 65.1% DCR. Additionally, 34.9% (15/43) of patients had disease control time ≥6 months (Table 3).

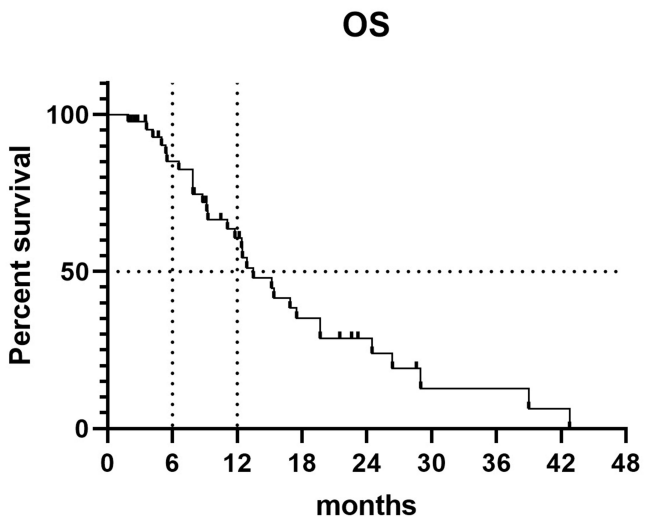

Figure 1 Kaplan–Meier survival curves of overall survival (OS).

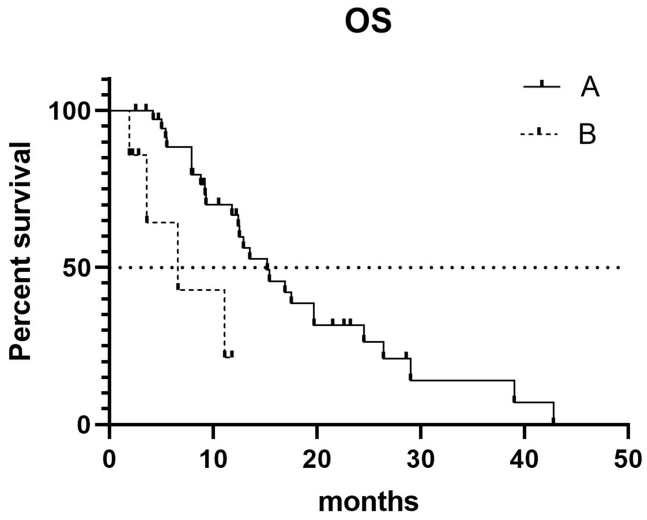

Figure 2 Kaplan–Meier survival curves of overall survival (OS) by treatment history (A: previously treated with both VEGF inhibitors and S-1; B: not previously treated with both VEGF inhibitors and S-1).

Safety

All patients initially received the full dose of raltitrexed and S-1 plus bevacizumab. Dose reductions were required in four (9.1%) patients.

Treatment-related AEs (TRAEs) are summarized in Table 4. Notably, 39/44 (88.6%) patients experienced at least one TRAE; TRAEs with a frequency of more than 5% were leukopenia (15.9%), nausea (15.9%), neutropenia (11.4%), thrombocytopenia (11.4%), gastrointestinal reactions (9.1%), and fatigue (6.8%). Most TRAEs were grades 1–2, but four (9.1%) patients experienced grades 3−4 TRAEs, including one (2.3%) case of grade 3 diarrhea, two (4.5%) of grade 3 thrombocytopenia, and one (2.3%) of grade 4 leukopenia. Both S-1 dose reduction and discontinuation were required in one (2.3%) patient. Overall, no treatment-related deaths occurred in this cohort.

Discussion

Despite the limited clinical evidence for the efficacy of the treatment regimen comprising raltitrexed plus S-1 and bevacizumab, this study showed the clinical benefit and toxicity profile of this combination for patients with refractory

Table 2 Multivariate Analysis of the Effect of the Chosen Parameters on OS

Parameters		HR	95% CI	p-value
CEA	≤42.8 ng/mL >42.8 ng/mL (ref)	0.382	0.153−0.952	0.039
Peritoneum metastases	No Yes (ref)	0.160	0.048−0.531	0.003
History of VEGF inhibitors and S-1	No Yes (ref)	0.215	0.059−0.785	0.020
Primary location	Left Right (ref)	0.385	0.166−0.897	0.089
***BRAF*^{V600E}**	Wild Mutation (ref)	0.059	0.010−0.358	0.609

Abbreviations: CEA, carcinoembryonic antigen; VEGF, vascular endothelial growth factor; OS, overall survival; HR, hazard ratio; CI, confidence interval; REF, reference.

metastatic CRC in a clinical real-world setting. The long-term and short-term efficacy achieved by this combination in the present study were comparable to previous studies regarding third-line treatments (Supplementary Tables S1). Obviously, it is not difficult to find that the 7% ORR of Raltitrexed plus S-1 and bevacizumab had the edge on that of Regorafenib, fruquintinib, TAS102 and TAS102/Bev ranging from 0% to 4.7%,[7–14] and the DCR of 65.1% seemed slightly superior to Regorafenib, and TAS102 monotherapy,[7,8,10,11] and evenly matched with fruquintinib and TAS102/Bev.[9,13,14] The PFS was extended by 1–2 months and OS by 4–7 months compared with Regorafenib, fruquintinib monotherapy,[7–9] and had certain advantage over TAS102/Bev in OS.[13,14] However, since these results are based on indirect comparison, they should be carefully interpreted.

In their 2019 Phase II study, Chen et al reported that S-1 combined with raltitrexed had a moderate effect on refractory metastatic CRC, with an ORR of 13.9%, DCR of 58.1%, PFS of 107 days (95% CI 96.3−117.7), and OS of 373 days (95% CI 226.2−519.8).[34] Recently, in 2021, the same group reported another Phase II trial, which showed that S-1 and raltitrexed combined with bevacizumab had promising antitumor activity and safety in refractory metastatic CRC. The ORR, DCR, PFS, and OS were 15.9%, 54.5%, 110 days (95% CI 65−155), and 367 days (95% CI 310.4−423.6), respectively.[35] These two trials by Chen with similar sample to the present study achieved relatively better tumor response probably because more patients in the present cohort have received much heavily previous treatment and fewer patients had no prior anti-VEGF treatment. Nevertheless, the disease control and survival benefits are consistent

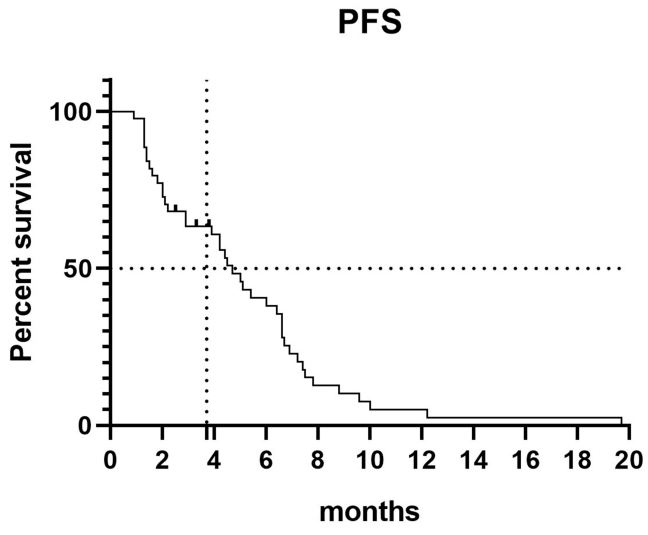

Figure 3 Kaplan–Meier survival curves of progression-free survival (PFS).

Table 3 Response of Patients with Measurable Disease (N = 43)

RECIST Response	Patients, n (%)
CR	0
PR	3 (7.0)
SD	25 (58.1)
PD	15 (34.9)
NE	1 (2.3)
ORR	3 (7.0)
DCR	25 (65.1)
DCR ≥ 6 months	15 (34.9)

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE; not evaluable; ORR, objective response rate; DCR, disease control rate.

Table 4 Adverse Events

Adverse Event	Grade, n (%)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AEs	39 (88.6)	13 (29.5)	22 (50)	3 (6.8)	1 (2.3)
Decreased appetite	1 (2.3)	0	1 (2.3)	0	0
Nausea	7 (15.9)	6 (13.6)	1 (2.3)	0	0
Vomiting	2 (4.5)	1 (2.3)	1 (2.3)	0	0
Diarrhea	1 (2.3)	0	0	1 (2.3)	0
Abdominal distension	1 (2.3)	1 (2.3)	0	0	0
Abdominal pain	2 (4.5)	0	2 (4.5)	0	0
Oral mucositis	1 (2.3)	1 (2.3)	0	0	0
Skin pigmentation	1 (2.3)	1 (2.3)	0	0	0
Fatigue	3 (6.8)	1 (2.3)	2 (4.5)	0	0
Rash	1 (2.3)	0	1 (2.3)	0	0
Leukopenia	7 (15.9)	1 (2.3)	5 (11.4)	0	1 (2.3)
Neutropenia	5 (11.4)	0	5 (11.4)	0	0
Thrombocytopenia	5 (11.4)	1 (2.3)	2 (4.5)	2 (4.5)	0
Elevated ALT/AST	1 (2.3)	0	1 (2.3)	0	0
Incomplete intestinal obstruction	1 (2.3)	0	1 (2.3)	0	0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; AE, adverse event.

with the results of the present study (Supplementary Tables S1). In this study, the survival benefits achieved by raltitrexed and S-1 plus bevacizumab were quite meaningful, given that almost one-third of patients in this cohort had undergone four lines of treatment and almost half had recently progressed to a treatment regimen comprising fluoropyrimidine.

Concordant with previous studies, this study indicated that raltitrexed could benefit patients with metastatic CRC exhibiting fluoropyrimidine resistance.[28–30]

In the exploratory multivariable regression analysis of potential prognostic factors, previous treatment with both VEGF inhibitors and S-1 (used either separately or combinedly early or late) significantly compromised the OS benefit from raltitrexed and S-1 plus bevacizumab. However, prior use of only raltitrexed or S-1 did not seem to significantly affect the subsequent benefits to the patient from this combination. This proves once again that raltitrexed and S-1 will not be completely cross-resistant, patients who have used only one of them can still benefit from their synergism. Although we cannot identify whether it is only the drug that have not been previously used in this combination that is working. At present, there is no clinical trial data to indicate this. Additionally, the clinical benefit was maintained irrespective of prior treatment with VEGF inhibitors, including bevacizumab and TKI, which was consistent with previous trials.[7–9,36–40] However, these results should be interpreted with critical thinking due to the small sample size in our cohort and the great heterogeneity in previous regimens.

Subgroup analysis revealed that patients with $BRAF^{V600E}$ mutations or peritoneal metastases had relatively shorter OS and that peritoneal metastasis was an independent prognostic factor for poor OS. However, no significant effect was evident in *RAS* mutational status or liver metastases. A recent study has demonstrated that primary tumor locations differ with respect to clinicopathological and molecular characteristics, as well as prognosis.[41] In the present study, subgroup analysis suggested a significant improvement in OS for patients with primary tumors located on the left side compared to the right side; however, no significant difference was detected in the multivariate Cox analysis.

Additionally, this study suggested that the OS of patients with a baseline CEA level below the median value of 42.8 ng/mL was significantly longer than that of patients with a higher CEA, which was consistent with previous findings.[42–45] Furthermore, a significantly prolonged PFS was observed in patients with higher LMR. Several studies have demonstrated the potential of LMR as an independent prognostic factor for several cancers; a high LMR is associated with higher OS;[46] however, no relationship was found between OS and LMR in this study. Therefore, the potential prognostic role and the cut-off values of CEA and LMR for refractory metastatic CRC warrant further investigation.

Regarding safety, the raltitrexed and S-1 plus bevacizumab combination was well-tolerated in this cohort. Most AEs were of grades 1−2, which were generally manageable. The most common AEs, such as nausea, leukopenia, neutropenia, and thrombocytopenia, were consistent with the previous Phase II trial of raltitrexed combined with S-1.[34] Compared to regorafenib and fruquintinib, raltitrexed and S-1 plus bevacizumab showed different toxicity profiles, suggesting that this regimen presents an alternative therapeutic option for patients unsuitable for receiving TKI.

Finally, this single-center, Chinese retrospective study with a small sample has some limitations. Thus, the subgroup analysis should be considered exploratory, and the results should be interpreted carefully. The lack of a control group also prevents confirmation of the study treatment effect. Thus, prospective, randomized controlled trials are warranted to further confirm the utility of the combination of raltitrexed and S-1 plus bevacizumab.

Conclusion

Raltitrexed and S-1 plus bevacizumab showed a favorable toxicity profile and promising efficacy in a real-world setting, which was comparable with the results of Phase II trials. Collectively, this study suggests that the studied combination is an alternative treatment option for patients with metastatic CRC who have been refractory or intolerant to standard therapies or for whom other treatment options are considered not to be available or feasible. It also provides evidence for the potential of peritoneal metastases, a high CEA value (>42.8 ng/mL), and previous treatment with both VEGF inhibitors and S-1 as independent poor prognostic factors.

Abbreviations

CRC, Colorectal cancer; OS, Overall survival; ORR, Objective response rate; PFS, Progression-free survival; DCR, Diseases control rate; AEs, Adverse events; CI, confidence interval; VEGF, vascular endothelial growth factor inhibitors; MSI, microsatellite instability; MMR, mismatch repair; TKI, tyrosine kinases inhibitor; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; CEA, carcinoembryonic antigen; LMR, lymphocyte/monocyte ratio; HR, hazard ratios; EGFR, epidermal growth factor receptor; TRAEs, Treatment-related AEs; BID, bis in die.

Data Sharing Statement

All data and/or materials used during this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All procedures performed in this study were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College (approval number: 2022062208472502). Given that this was a retrospective study, the requirement for informed consent was waived by the Ethics Committees of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College. Patient data was anonymized for confidentiality.

Acknowledgments

We would like to express our sincere thanks to all the team members who provided help during the research process. Thanks also to the Editage (www.editage.cn) for English language editing. No financial support was received for the study, authorship, and/or publication of this paper.

Author Contributions

All authors made a significant contribution to conception, study design, execution, acquisition of data, analysis, and interpretation or in all these areas; took part in drafting, revising or critically reviewing the article; have agreed on the journal to which the article was submitted, gave the final version accepted for publication and agree to take responsibility for the contents of the work.

Funding

This work was supported by the Development Project of Medical Oncology Key Foundation of Cancer Hospital Chinese Academy of Medical Sciences (CICAMS-MODP2022002).

Disclosure

All authors have no conflict of interest regarding this study.

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