Observational Study

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Apatinib as an optional treatment in metastatic colorectal cancer

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Abstract

Antiangiogenic therapy has shown clinical benefit in metastatic colorectal cancer (mCRC). We aimed to evaluate the efficacy and safety of apatinib in patients who failed standard treatment and to explore potential factors related to its efficacy.

A total of 47 patients were enrolled in this retrospective study. Patients who received apatinib therapy after failure of standard therapy from December 2014 and February 2018 were included. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and treatment-related adverse events were recorded and evaluated.

The median PFS was 3.717 months (95% confidence interval [CI], 3.198–4.235), and the median OS was 7.335 months (95% CI, 6.738–7.932). The disease control rate was 72.34%, and the ORR was 8.51%. The most common grade 3 to 4 adverse reactions were hypertension, proteinuria, hand-foot syndrome, and diarrhea. Multivariate analysis indicated previous antiangiogenic therapy and baseline elevated neutrophil-to-lymphocyte ratio (NLR) as independent prognostic factors.

Apatinib might be a reasonable treatment option with a controlled safety profile for patients with mCRC who have failed standard therapy. Patients who previously received antiangiogenic therapy and who have baseline elevated NLR are more likely to benefit from apatinib.

Abbreviations: AEs = adverse events, AUC = area under the curve, CI = confidence interval, DCR = disease control rate, HRs = hazard ratios, mCRC = metastatic colorectal cancer, NLR = neutrophil-to-lymphocyte ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PLR = platelet-to-lymphocyte, VEGF = vascular endothelial growth factor, WT = wild-type.

Keywords: apatinib, colorectal cancer, efficacy, safety

1. Introduction

Colorectal cancer (CRC) is the fifth most common malignancy in China,[1] and remains the second cause of cancer death worldwide.[2] Although surgical resection of metastatic lesions can significantly extend life and improve the quality of life, most patients lose the opportunity to receive radical surgery because of the presence of multiple metastatic sites. Systemic cytotoxic chemotherapy has become an important treatment option for metastatic CRC (mCRC).[3] In addition, molecular-targeted therapeutic drugs (cetuximab, bevacizumab, aflibercept, regorafenib, and ramucirumab) have been approved by the Food and Drug Administration for the treatment of mCRC.[3] Although many innovative drugs have been developed, some studies found that, in the case of mCRC, the median overall survival (OS) was no more than 41.3 months, and the median progression-free survival (PFS) was only 13.0 months.[4] Although most patients will experience undesired progressive disease, it is necessary to explore effective treatment options for these patients.

The vascular endothelial growth factor–A (VEGF-A)/VEGFR-2 signal pathway is regarded as a key limiting step in tumor growth and metastasis. A variety of antiangiogenesis approaches targeting the VEGF-A/VEGFR-2 signal pathway have shown modest improvements in the OS and PFS associated with mCRC.[5] Apatinib is a small-molecule tyrosine kinase inhibitor that highly selectively binds to and strongly inhibits VEGFR2. In 2014, the China Food and Drug Administration approved apatinib for the treatment of chemotherapy-refractory advanced and metastatic adenocarcinoma of the stomach and gastroesophageal junction.[6,7] Subsequently, apatinib showed extensive antitumor effects, including breast cancer,[8] lung cancer,[9,10] and esophageal cancer.[11] Some preclinical trials and clinical trials have shown apatinib to be effective in treating mCRC,[12–14] but the published literature is still limited. Meanwhile, factors associated with the effect of apatinib are still unclear.

Therefore, we carried out this observational study to provide additional clinical evidence for apatinib treatment in patients with mCRC and to explore possible factors associated with its antiangiogenesis efficacy.

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AL and KW contributed equally to this work.

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2. Materials and methods

Patients with pathologically confirmed advanced and mCRC were eligible. All patients had progressed and relapsed after undergoing at least 1 line of systemic therapy according to guidelines of the National Comprehensive Cancer Network. A total of 47 patients were enrolled between December 2014 and February 2018. All patients had received ≥1 cycle of apatinib therapy and were eligible for efficacy and toxicity assessments. Exclusion criteria were follows:

(1) renal insufficiency, heart insufficiency and severe pulmonary dysfunction;
(2) active infective or sepsis;
(3) active visceral hemorrhage;
(4) gastrointestinal perforation or obstruction;
(5) high risk of bleeding (prothrombin time ≥ 12.9 seconds, active partial thromboplastin time ≥ 38.4 seconds);
(6) inadequate bone marrow function (white blood cells ≤3000/μL, platelet count ≤50000/μL).

All patients were informed of the use of apatinib. They provided written consent before treatment and consented to the use of their treatment process data for future medical research. This study was approved by the Second People's Hospital of Lianyungang's review boards and ethics committees after a careful review of the ethical and scientific aspects.

2.1. Clinical-pathological and laboratory data

Clinical-pathological data were retrospectively obtained from patients' medical histories. Blood values including leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts were collected and counted by flow cytometry before the treatment of apatinib. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. The platelet-to-lymphocyte (PLR) was calculated as the absolute platelet count divided by the absolute lymphocyte count.

2.2. Treatment

Apatinib therapy was initiated from an oral administration dosage of 500 mg once a day, 4 weeks for a cycle, which could be decreased to 250 mg once daily according to the patients' actual performance status and the patients' severe adverse events (AEs). The chemotherapy combined with apatinib was based on the physicians' determination of the patient's situation. Treatment interruption, resulting from AEs, was allowed for no more than 14 days. Patients received treatment until disease progression, development of unacceptable toxicity, death, and discontinuation of apatinib for any other reason.

2.3. Assessments

Patients with measurable disease were evaluated by response evaluation criteria in solid tumors. All patients underwent computed tomography scan at baseline, after 1 cycle, and after every 2 cycles and progression of the disease. Disease control was defined as complete remission, partial remission, and stable disease. Patients in whom the disease progressed after 2 cycles of treatment were defined as having progressive disease. PFS was defined as the time between the start of the treatment and disease progression and death (the first event that occurs) and last tumor evaluation. OS was considered as the duration from the start of therapy with apatinib to the date of death and the last day of follow-up. AEs were graded according to the NCI Common Toxicity Criteria version 3.0.

2.4. Statistical analysis

R 3.4.2 software was used to determine the cutoff value for pretreatment levels of NLR and PLR by survival ROC data package. The results showed that the area under the curve (AUC) of NLR was 0.731 and the AUC of PLR was 0.439. Thus, NLR levels were analyzed further.

The PFS and OS after treatment were estimated by the Kaplan–Meier method. The comparison of subgroup analysis was applied using a log-rank test. The hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs) were estimated using the Cox's proportional hazards regression model, and the results were displayed in a forest plot.

Both responses and AEs were aggregated in the form of frequency counts and percentages. The objective response rate (ORR) and disease control rate (DCR) analyses were based on frequency counts. The proportion of patients with an ORR was compared using Fisher exact test.

All statistical analyses were performed using SPSS for windows (version 20, IBM, Armonk, NY).

3. Results

3.1. Patients and tumor characteristics

The main clinic-pathological characteristics of the 47 patients are shown in Table 1. All patients had received previous treatment, including mFOLFOX6, FOLFORI, and XELOX. Eleven (23.4%) patients received bevacizumab, and the remaining patients received no target therapy. Twenty-seven (57.4%) patients were administered apatinib in combination with chemotherapy, mainly with raltitrexed or tegafur, and 20 (42.6%) patients received apatinib alone.

3.2. Efficacy

All 47 patients were evaluated by image examination. Four patients achieved partial remission, 30 patients had stable disease, and 13 patients were reported as progressive disease after the apatinib therapy. These resulted in an ORR of 8.51% and a DCR of 72.34% (Fig. 1A and B), and factors considered as potential markers associated with the efficiency, such as Eastern Cooperative Oncology Group performance status, peritoneal metastasis, number of metastases, and apatinib combination, did not make any differences in our study, probably because of the small sample size and the lack of effect of apatinib on these patients (Table 1).

At the time of analysis, 45 patients had progressed from apatinib therapy and 39 patients had died mainly because of tumor progression. The median PFS was 3.717 months (95% CI, 3.198–4.235), and the median OS was 7.335 months (95% CI, 6.738–7.932) (Fig. 1C and D).

As shown in Table 2, we found prior antiangiogenic therapy and baseline NLR was associated with PFS and OS (Fig. 2). To explore possible factors associated with the effect of apatinib, we brought patients' characteristics into our analysis model. The

Table 1

Patient characteristic at baseline.

Patient characteristic	Value (n. %)	ORR			P
		PR (n. %)	SD (n. %)	PD (n. %)	
Age (yr)					.810
<65	25 (53.2)	2 (8.0)	17 (68.0)	6 (24.0)	
≥65	22 (46.8)	2 (9.1)	13 (59.1)	7 (31.8)	
Gender					.232
Male	31 (66.0)	4 (12.9)	20 (64.5)	7 (22.6)	
Female	16 (34.0	0 (0.0)	10 (62.5)	6 (37.5)	
ECOG PS					.887
0,1	20 (42.6)	2 (10.0)	12 (60.0)	6 (30.0)	
2,3	27 (57.4)	2 (7.4)	18 (66.7)	7 (25.9)	
Cancer site					.158
Right	19 (40.4)	0 (0.0)	12 (63.2)	7 (36.8)	
Left	28 (59.6)	4 (14.3)	18 (64.3)	6 (21.4)	
Tumor invasion					.895
T1+T2	9 (19.1)	1 (11.1)	6 (66.7)	2 (22.2)	
T3+T4	38 (80.9)	3 (7.9)	24 (63.2)	11 (28.9)	
Lymph node invasion					.181
N0	10 (21.2)	1 (10.0)	6 (60.0)	3 (30.0)	
N1	17 (36.2)	3 (17.6)	12 (70.6)	2 (11.8)	
N2	20 (42.6)	0 (0.0)	12 (60.0)	8 (40.0)	
Differentiation					.982
Well	9 (19.1)	1 (11.1)	5 (55.6)	3 (33.3)	
Moderate	24 (51.1)	2 (8.3)	16 (66.7)	6 (25.0)	
Low	14 (29.8)	1 (7.1)	9 (64.3)	4 (28.6)	
Metastatic site					.679
Lung	14 (29.8)	2 (14.3)	8 (57.1)	4 (28.6)	
Liver	15 (31.9)	0 (0.0)	11 (73.3)	4 (26.7)	
Peritoneum	18 (38.3)	2 (11.1)	11 (61.1)	5 (27.8)	
No. of metastatic sites					.502
<2	12 (25.5)	2 (16.7)	7 (58.3)	3 (25.0)	
≥2	35 (74.5)	2 (5.7)	23 (65.7)	10 (28.6)	
Bevacizumab prior to apatinib					.997
Yes	11 (23.4)	1 (9.1)	7 (63.6)	3 (27.3)	
No	36 (76.6)	3 (8.3)	23 (63.9)	10 (27.8)	
Apatinib combined					.161
Yes	20 (42.6)	0 (0.0)	13 (65.0)	7 (35.0)	
No	27 (57.4)	4 (14.8)	17 (63.0)	6 (22.2)	
CEA					.105
<6	14 (29.8)	3 (21.4)	7 (50.0)	4 (28.6)	
≥6	33 (70.2)	1 (3.0)	23 (69.7)	9 (27.3)	
CA199					.440
<37	25 (53.2)	3 (12.0)	14 (56.0)	8 (32.0)	
≥37	22 (46.8)	1 (4.6)	16 (72.7)	5 (22.7)	
NLR					.071
<3.33	23 (49.0)	3 (13.0%)	17 (73.9)	3 (13.1%)	
≥3.33	24 (51.0)	1 (4.1%)	13 (54.2%)	10 (41.7%)	

Cox regression model showed a significant association between the PFS of apatinib therapy and prior antiangiogenic therapy (adjusted HR, 0.382; 95% CI, 0.153–0.955; $P = .040$) and baseline NLR (adjusted HR, 0.423; 95% CI, 0.192–0.932; $P = .033$) (Fig. 3). The OS also had a similar result as PFS (Fig. 3).

3.3. Adverse events

The main toxicities possibly related to therapy are listed in Table 3. The AEs in the 47 patients were generally mild, mainly ranging from grade 1 to grade 2. Six patients experienced grade 3 AEs, including hypertension, proteinuria, hand-foot syndrome, and diarrhea. There were no grade 4 AEs in our analysis. None of the patients died of drug-related causes during the study period.

4. Discussion

Our study is a real-world observation of the efficacy and safety of apatinib therapy for patients with mCRC. In this study, apatinib therapy led to a median PFS of 3.717 months (95% CI, 3.198–4.235), a median OS of 7.335 months (95%CI 6.738–7.932), an ORR of 8.51%, and a DCR of 72.34%. Common AEs were hypertension (51.06%), proteinuria (44.68%), and neutropenia (22.76%). The most severe AEs (>grade 3) were hypertension (8.51%), proteinuria (4.26%), and diarrhea (4.26%). Our results seemed to be different from 2 recent studies of apatinib in mCRC patients.[11,12] However, there were some bright spots in our study. On one hand, patients' performance status before apatinib in this study was much worse. These discrepancies illustrated that

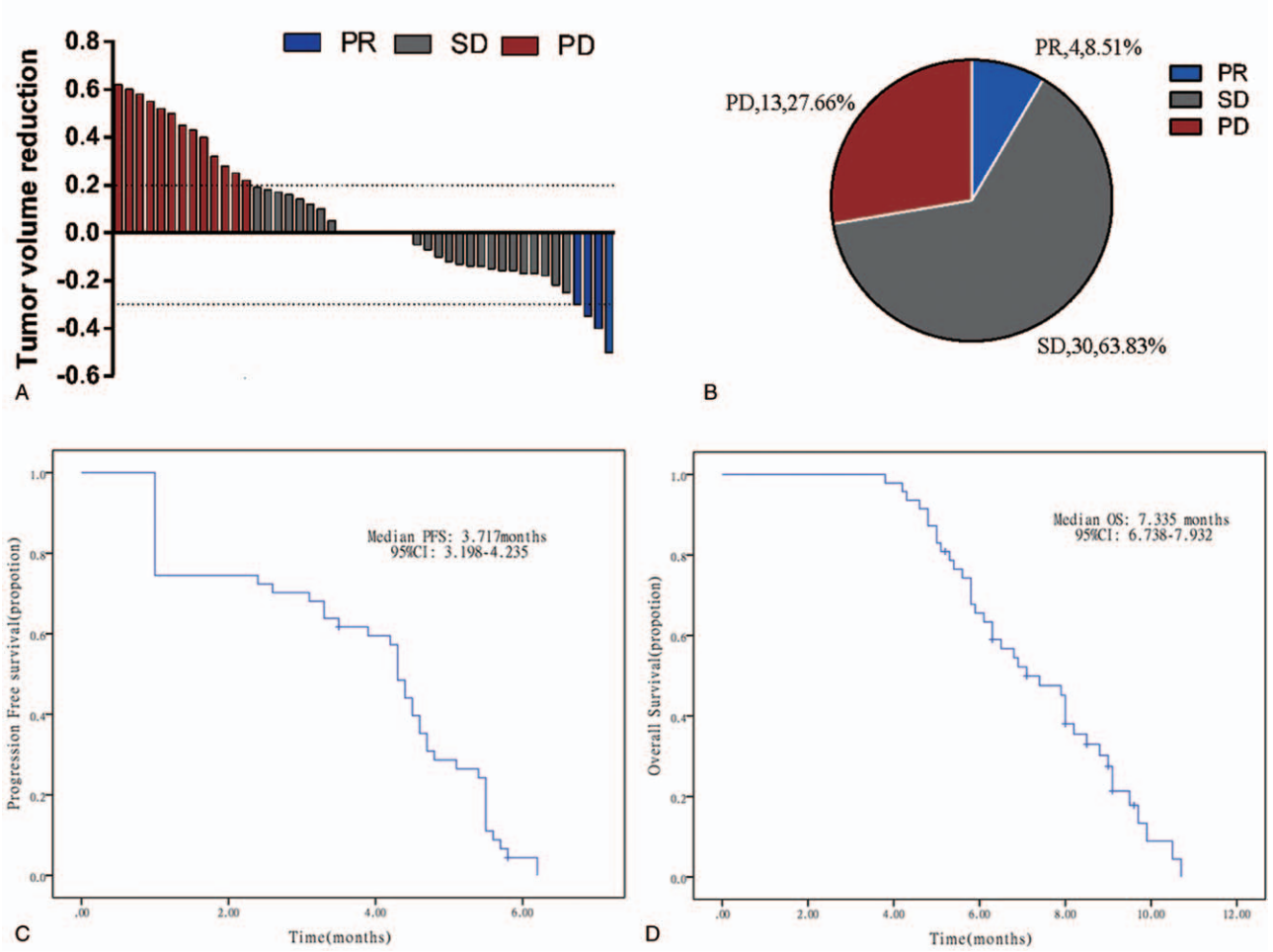

Figure 1. Potentiation of antitumor activity of apatinib in mCRC patients. Notes: (A) Best percentage changed from baseline in measurable tumor lesions showed by waterfall plot; (B) Objective response rate showed by Pie chart; (C) Kaplan–Meier survival curve of PFS of the patients from apatinib treatment; (D) Kaplan–Meier survival curve of OS of the patients from apatinib treatment. mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression free survival.

patients in the real world have worse performance status and have more visceral metastasis and higher tumor burden, highlighting the gap between the randomized controlled trials and real-world treatment. On the other hand, combination with other therapy was allowed according to patients' actual performance status in our study, which was not covered in trials. We believe that these rectifications may be beneficial for obtaining similar results with previous trials, even if patients were heavily pretreated and performed worse. Moreover, these rectifications, especially combination chemotherapy, did not increase the incidence of AEs, which indicates adequate tolerance of patients.

Preclinical data demonstrated that vascular endothelial growth factor was continuously expressed during oncogenesis, tumor growth, and metastasis, and prolonged exposure to VEGF inhibitors could delay tumor growth and even prevent tumor angiogenesis.[15] Continuous angiogenic blockade strategy has been evaluated in the clinical setting and has proven to benefit patients with mCRC.[16–18] However, some conflicting results were reported for maintenance treatment with bevacizumab during chemotherapy-free intervals in mCRC,[19] partly indicating that patients benefit from continuous antiangiogenic therapy only. In our exploratory analysis, multivariate analysis suggested prior antiangiogenic therapy was an independent factor associated with the PFS of apatinib therapy. Although the benefit of bevacizumab was not testified in maintenance treatment, reintroduction of bevacizumab after progression to first-line therapy still prolongs OS in mCRC. Furthermore, bevacizumab plus thermotherapy extended survival time more than cetuximab after progression with bevacizumab plus thermotherapy in patients with wild-type (WT) KRAS mCRC.[16] These results show that, until now, continuous angiogenic blockade strategy may have been a rational choice.

Antiangiogenic therapies, whether monoclonal antibodies or tyrosine kinase inhibitors, is usually combined with chemotherapy because of their poor efficiency when used alone. Preclinical models demonstrated that sustained monoclonal antibody antiangiogenic treatment could create and remodel an environment suitable for normalization of stable vascular endothelial cells, leading to increasing tumor uptake of chemotherapy, which could be a possible explanation for the beneficial effect of this combination therapy.[20] Miaomiao Gou et al recently demonstrated that there was no clear survival benefit of apatinib combined with chemotherapy as compared with apatinib

Table 2

Exploratory analysis of factors to predict PFS and OS of apatinib.

		mPFS			mOS		
group	n	median	95%CI	P	median	95%CI	P
Age (years)							0.721
<65	25	3.855	3.127–4.583	.323	7.407	6.550–8.264	
≥65	22	3.564	2.812–4.316		7.261	6.414–8.108	
Gender							.415
Male	31	3.928	3.293–4.564	.186	7.612	6.911–8.313	
Female	16	3.313	2.418–4.207		6.803	5.698–7.907	
ECOG PS							.684
0,1	20	3.605	2.689–4.521	.470	7.407	6.434–8.380	
2,3	27	3.776	3.190–4.363		7.257	6.516–7.999	
Cancer site							.408
Right	19	3.505	2.574–4.436	.759	6.918	5.979–7.856	
Left	28	3.842	3.242–4.441		7.597	6.834–8.360	
Tumor invasion				.812			.482
T1+T2	9	3.332	1.996–4.648		6.951	5.751–8.151	
T3+T4	38	3.800	3.238–4.361		7.412	6.745–8.079	
Lymph node invasion				.806			.177
N0	10	3.360	2.006–4.714		6.950	5.831–8.069	
N1	17	4.118	3.433–4.802		8.130	7.190–9.069	
N2	20	3.530	2.693–4.368		6.802	5.907–7.697	
Differentiation							.627
Well	9	4.100	2.916–5.284	.518	7.459	6.541–8.378	
Moderate	24	3.829	3.092–4.566		7.447	6.583–8.312	
Low	14	3.280	2.327–4.233		6.907	5.777–8.037	
Metastatic site							.626
Lung	14	3.893	2.981–4.804	.994	7.139	6.258–8.020	
Liver	15	3.573	2.672–4.475		7.275	6.159–8.391	
Peritoneum	18	3.679	2.798–4.561		7.435	6.353–8.517	
No. of metastatic sites							.652
<2	12	3.876	2.761–4.991	.524	7.271	6.193–8.348	
≥2	35	3.666	3.073–4.259		7.359	6.639–8.079	
Prior antiangiogenic therapy							.017
Yes	11	4.545	3.437–5.654	.012	8.604	7.217–9.990	
No	36	3.459	2.890–4.027		6.938	6.325–7.552	
Apatinib combined							.555
Yes	20	3.475	2.573–4.377	.717	6.842	5.783–7.901	
No	27	3.891	3.278–4.504		7.674	7.014–8.334	
CEA							.558
<6	14	3.714	2.698–4.730	.933	6.996	6.081–7.912	
≥6	33	3.717	3.106–4.328		7.419	6.695–8.144	
CA199							.107
<37	25	3.704	3.028–4.380	.324	6.985	6.296–7.675	
≥37	22	3.740	2.920–4.560		7.732	6.735–8.729	
NLR							.006
<3.33	23	4.336	3.657–5.016	.035	8.182	7.313–9.050	
≥3.33	24	3.108	2.420–3.796		6.532	5.847–7.216	

alone,[12] which corresponds with our results. However, bevacizumab combined chemotherapy was a priority recommended alternative to patients with KRAS WT mCRC.[21–23]

Another study reported that the addition of regorafenib to FOLFIRI as second-line therapy for mCRC only modestly prolonged PFS when compared with FOLFIRI alone.[24] Some preclinical studies showed that apatinib significantly enhanced the cytotoxicity of substrate drugs and increased the intracellular accumulation of chemotherapy drugs by reversing multidrug resistance.[25,26] Further studies were warranted.

Our results show that NLR at baseline has an independent prognostic impact on patients treated with apatinib; that, is patients with NLR ≥3.33 have a worse prognosis than those with NLR <3.33. The mechanism underlying the association between high NLR and worse outcome has not been clearly identified, but it could be due to the association of NLR with inflammation.[27] Neutrophils can inhibit the immune system, abolishing the function of immune cells.[28] Meanwhile, these cells can promote adhesion and seeding of distant organ sites through the secretion of circulating growth factors, such as VEGF and proteases.[29] On the other hand, lymphocytes play a crucial role in tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration, thereby dictating the host's immune response to malignancy.[30] Recently, 1 study confirmed the prognostic role of NLR in patients with mCRC treated with bevacizumab plus chemotherapy as first-line therapy, showing

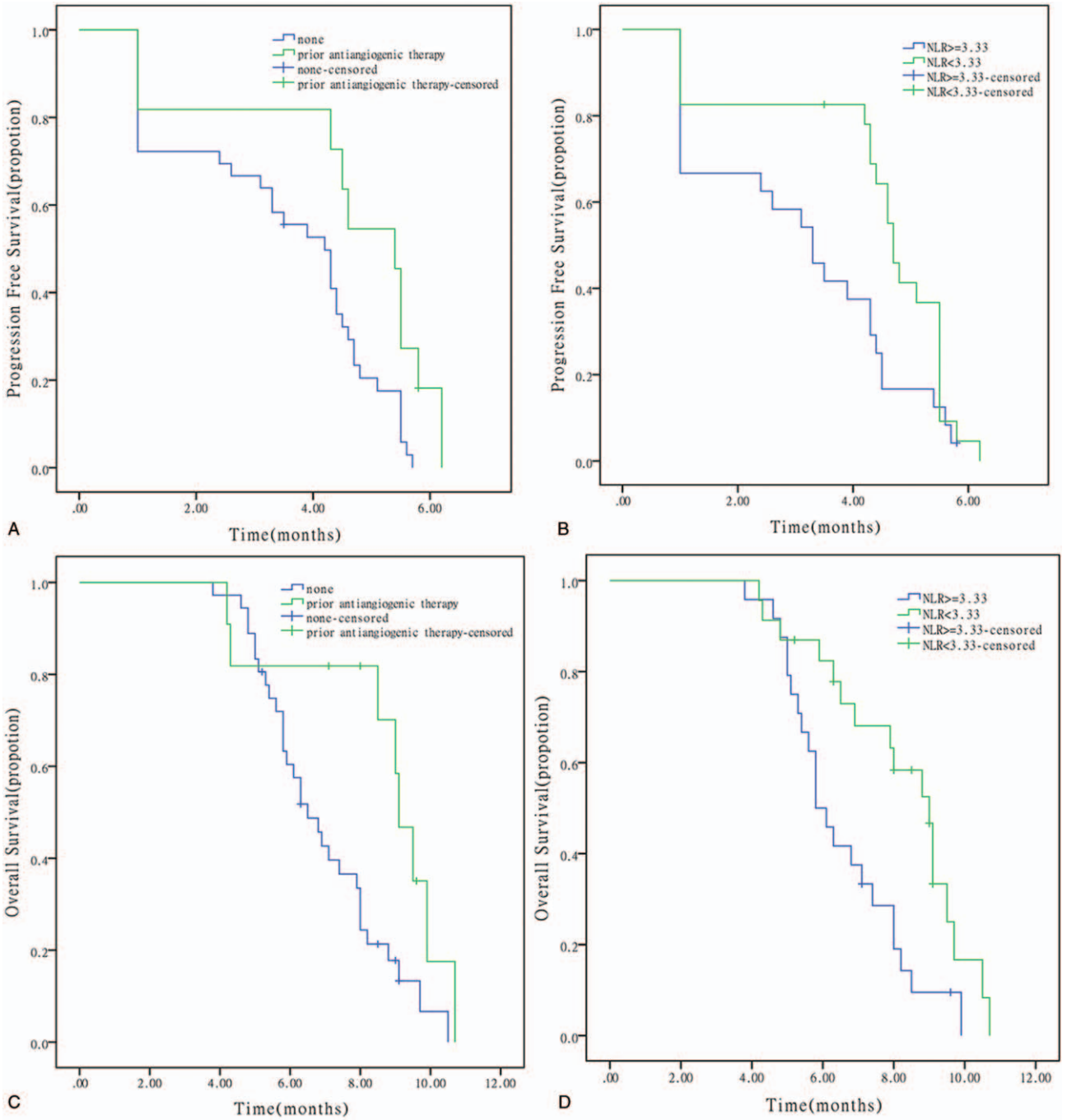

Figure 2. Kaplan–Meier estimates of subgroup analyses. Notes: (A) and (C) were estimated for patients with and without prior antiangiogenic therapy. (B) PFS and (D) OS were estimated for patients with different NLR levels. NLR = neutrophil to lymphocyte ratio, OS = overall survival, PFS = progression free survival.

the worse prognosis of patients with high NLR.[31] Our results were consistent with previous studies,[32] further supporting NLR as a good prognostic and predictive marker for mCRC patients treated with chemotherapy plus antiangiogenesis therapy.

Angiogenesis is a complicated process by various pro- and anti-angiogenic factors, which is critical for tumor development and growth, while VEGF is a crucial regulator in this process. Until now, disrupting VEGF signaling is a major approach in anti-angiogenesis treatment. So, some factors relevant with this signal pathway are regarded as potential predictive biomarkers for anti-angiogenic therapies. Recently, Gurzu S et al revealed the most indicated cases for anti angigenic therapy seem to be the pN0 and pN1 cases in the rectum and sigma, respectively pN0 and pN2 cases in the right colon,[33] emphasizing lymph node invasion is important in angiogenesis. Unfortunately, our study did not verify this deduction. A big and robust study maybe is warranted. However, consistent with the result the ratio CD31/CD105 differences between descendent and right or left colon were not observed, our study also presented that tumor location was not related to efficacy of anti-angiogenic treatment.

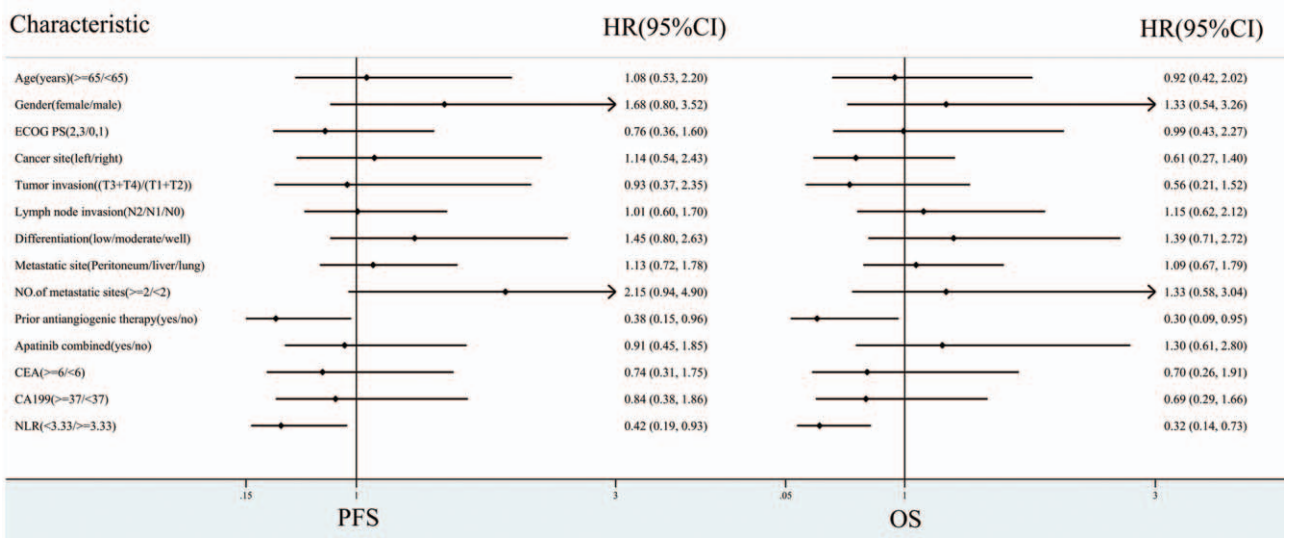

Figure 3. Subgroup analyses of PFS and OS showed by forest plot. Notes: ECOG PS = Eastern Cooperative Oncology Group performance status, HR = hazard ratio, NLR = neutrophil to lymphocyte ratio, OS = overall survival, PFS = progression free survival.

Although apatinib is associated with improved PFS and DCR, it also exposes patients to its toxicity. This toxicity has drawn the increasing attention of physicians and patients before consideration of the administration of apatinib. Hypertension, proteinuria, and hand-foot syndrome are the most common AEs in antiangiogenic therapy. Our results indicate that apatinib does not increase the risks associated with antiangiogenic therapy and can be tolerated by patients with a heavy tumor burden of the primary lesion. In our clinical center, we have gathered plentiful experiences. When grade 2 proteinuria occurred, we administered prednisone, and the protein in the urine vanished. On the other hand, when grade 2 hand-foot syndrome occurred, a Chinese patent medicine called RONG ZHAO ZHI YANG capsule was offered, and the syndrome was obviously alleviated. On the whole, from the observations in our study and previous trials, we can see that the AEs of apatinib are manageable, based on physician awareness and patient education.

Table 3

Adverse events.

Adverse event	Grade 1–2 (n, %)	Grade 3–4 (n, %)	Total (n, %)
Non hematologic			
Hypertension	20 (42.60%)	4 (8.51%)	24 (51.06%)
Hand-foot syndrome	15 (31.91%)	2 (4.26%)	17 (36.17%)
Proteinuria	19 (40.42%)	2 (4.26%)	21 (44.68%)
Elevated transaminase	10 (21.28%)	0 (0%)	10 (21.28%)
ALP increased	5 (10.64%)	1 (2.10%)	6 (12.77%)
Hyperbilirubinemia	9 (19.15%)	0 (0%)	9 (19.15%)
Fatigue	11 (23.4%	1 (2.10%)	12 (25.53%)
Diarrhea	12 (25.53%)	2 (4.26%)	14 (29.79%)
Bleeding	5 (10.64%)	0 (0%)	5 (10.64%)
Mucositis	4 (8.51%)	0 (0%)	4 (8.51%)
Nausea and vomiting	21 (44.68%)	0 (0%)	21 (44.68%)
Hematologic			
Neutropenia	12 (25.53%)	1 (2.10%)	13 (27.66%)
Leukopenia	17 (36.17%)	1 (2.10%)	18 (38.30%)
Thrombocytopenia	13 (27.66%)	1 (2.10%)	14 (29.79%)
Anemia	9 (19.15%)	0 (0%)	9 (19.15%)

This study offers some baseline real-world efficacy and safety data for apatinib, which are informative for physicians and patients. Second, exploratory analysis provides several clues for the selection of patients who are more likely to benefit from apatinib. Third, safety analysis of this study indicates that the possible side effects of apatinib are acceptable. However, there are some limitations of our study. Some questions associated with its retrospective observational methodology have been raised, including potential missing data, possible information bias, small sample size, and lack of a control group. Moreover, the present study did not observe how drug-related AEs influence patients' quality of life. Further prospective studies are warranted to prove that apatinib can be a highly recommended targeting agent following bevacizumab treatment.

5. Conclusions

On the whole, our study found that patients with metastatic colorectal tumors, including patients previously treated with bevacizumab, can gain obvious benefit from apatinib therapy. Moreover, side effects from apatinib are controlled and are similar to those seen in other clinical trials. Some prospective studies are needed to validate the efficacy of apatinib and the role of the NLR in this process.

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