Third-line treatment for metastatic colorectal cancer: anlotinib is superior to chemotherapy and similar to fruquintinib or regorafenib

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The clinical efficiency and adverse reactions of anlotinib in metastatic colorectal cancer (mCRC) as a third-line treatment compared with chemotherapy and regorafenib or fruquintinib was explored in this study. Clinical data from 105 mCRC patients who failed at least two lines of chemotherapy were collected. The patients were divided into three groups based on their third-line therapeutic regimen: third-line chemotherapy only (group A); anlotinib (group B); and fruquintinib or regorafenib (group C). The result showed that the ORR and DCR of group B (14.29%, 85.71%) were higher than those of group A (0%, 40.00%). The ORRs of group B and group C were 14.29% and 20.00%, respectively. Group B and group C had the same DCR, 85.71%. The mean PFS values of group B (3.46 months) and group C (3.33 months) were longer than that of group A (2.25 months) (χ^2=84.255, p<0.001) and the mean PFS values of group B and group C were similar (χ^2=0.884, p=0.347). The mean OS of group B was 9.22 months, which was longer than that of group A (6.95 months) (χ^2=38.837, p<0.001). The mean OS values of group B (9.22 months) and group C (9.38 months) were not significantly different (χ^2=0.456, p=0.499). The incidences of proteinuria, hand-foot skin reaction, myelosuppression, and gastrointestinal reaction were similar between group B and group C (p=0.173, 0.188, 1.00, 0.154, respectively). Myelosuppression and gastrointestinal reaction were more common in group A than in group B and group C (p<0.001). For mCRC, anlotinib as a third-line treatment is better than chemotherapy and similar to regorafenib or fruquintinib. The associated adverse reactions are tolerable.

Key words: metastatic colorectal cancer, anlotinib, chemotherapy, fruquintinib; regorafenib

Colorectal cancer (CRC) is a common malignant tumor with the third highest mortality [1, 2]. In China, the incidence of CRC is increasing, with an average annual rate of 4–5%. In 2015, the number of new CRC cases and deaths caused by CRC doubled compared with the respective values 10 years ago, reaching 377,000 deaths and 191,100 cases, respectively [3, 4]. For metastatic colorectal cancer (mCRC), chemotherapy is a traditional and classic method. Common chemotherapy regimens include CAPOX, FOLFOX4, and FOLFIRI. However, only 30–40% of patients can benefit from antitumor chemotherapy due to the low response rate. Although the clinical efficacy is improved when chemotherapy is combined with antiangiogenic drugs such as bevacizumab or cetuximab, the 5-year survival rate of advanced CRC is only 1–2% [5, 6]. Moreover, standard third-line treatment is absent. Therefore, it is of great significance to find effective third-line targeted drugs for mCRC patients.

Receptor tyrosine kinases (RTKs) are transmembrane glycoproteins that communicate with cellular growth factors and extracellular ligands. They are crucial for intracellular tyrosine phosphorylation and intracellular signaling. Many vital physiological processes, including cell proliferation, cell growth, cell migration, cell differentiation, and apoptosis, are mediated by RTK activation, which is regulated by protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) [7]. There is no or low activity and expression of most oncogenic RTKs in normal tissues, while hyperactive RTKs or upregulated oncogenic RTK levels in malignant cells have been confirmed by researchers [8, 9]. Furthermore, in vitro, the downregulation of PTK activity can attenuate tumor cell growth, angiogenesis, and antiapoptotic effects [10].

Anlotinib is a newly approved orally administered small-molecule RTK inhibitor. It targets RTKs related to tumor proliferation and metastasis, including vascular endothelial growth factor receptor (VEGFR), c-proto-oncogene

protein, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) [11, 12]. VEGF isoforms and VEGFRs are crucial proteins in vasculogenesis and angiogenesis. Studies have provided enough evidence to support their clinical effect as anticancer targets [13–15]. *In vitro* studies using recombinant enzymes showed that anlotinib selectively inhibited VEGFR2/KDR and VEGFR3 approximately 20 and 500 times as potently as sunitinib and sorafenib, respectively. On the other hand, the FGF/FGFR axis can result in aggressive cancer phenotypes by promoting cancer progression and enhancing the angiogenic potential of the tumor microenvironment [16, 17]. Moreover, FGF/FGFR signaling alterations are closely associated with chemotherapy resistance and poor clinical outcome [18–21]. Preclinical results indicated that anlotinib significantly inactivated FGFR1–4, especially FGFR2, to a greater extent than did sorafenib.

Clinical trials have proven the effective anticancer activity of anlotinib in advanced non-small-cell lung cancer (NSCLC) [22, 23], advanced soft tissue sarcoma (STS) [24, 25], advanced medullary thyroid cancer (MTC) [26, 27], and metastatic renal cell carcinoma (mRCC) [28]. However, the anticancer activity of anlotinib as a third-line treatment for mCRC requires more evidence. Further exploration is needed to determine whether the clinical effect of anlotinib as a third-line treatment for mCRC is superior to that of chemotherapy and other targeted therapies, such as regorafenib and fruquintinib. In this research, we compared the clinical effects of anlotinib, chemotherapy, and fruquintinib or regorafenib as third-line treatments for metastatic colorectal cancer.

In this article, a retrospective clinical analysis was conducted with data from the First Affiliated Hospital of Dalian Medical University from January 1, 2018, to January 1, 2020, to explore the clinical efficacy and safety of anlotinib compared with chemotherapy and fruquintinib or regorafenib for mCRC patients who failed at least two lines of chemotherapy.

Patients and methods

Patient selection. Eligible patients were those who presented with mCRC who failed at least two lines of chemotherapy, and they were admitted to the First Affiliated Hospital of Dalian Medical University for third-line treatment from January 1, 2018, to January 1, 2020 (n=105). Patients were without cardiac, liver, and renal dysfunctions, and other malignant tumors. The Eastern Cooperative Oncology Group (ECOG) scores of the selected patients ranged from 0 to 3. The expected survival time was more than 3 months. In addition, those who had received traditional Chinese medicine in the past three months were not eligible.

Grouping. Patients were divided into three groups based on their third-line therapeutic regimen. Group A (n=35) received third-line chemotherapy only. The chemotherapy

regimen included irinotecan (from Hengrui Pharmacy Co. Ltd., Jiangsu. China; 300 mg/m² intravenous drip for more than 90 minutes on the first day of a 21-day cycle) combined with raltitrexed (from Nanjing Zhengda Tianqing Pharmaceutical Co. Ltd., China; 2.6 mg/m² intravenous drip for more than 15 minutes on the second day of a 21-day cycle) or raltitrexed only (Nanjing Zhengda Tianqing Pharmaceutical; 3 mg/m² intravenous drip for more than 15 minutes on the first day of a 21-day cycle). The chemotherapy regimen was decided by three or more oncologists based on the previous chemotherapy patients had been given. Group B (n=35) received anlotinib (Zhengda Tianqing Pharmaceutical; 12 mg/d *per os* from the first day to the fourteenth day of a 21-day cycle). Group C (n=35) received fruquintinib (Hutchison Whampoa Pharmaceutical Co. Ltd., Shanghai, China; 5 mg/d *per os* from the first day to the twenty-first day of a 28-day cycle) or regorafenib (Bayer Pharmaceutical Co. Ltd., Germany; 160 mg/d *per os* from the first day to the twenty-first day of a 28-day cycle).

Follow-up and data collection. Follow-up ended as result of death or relapse or on January 1, 2020. The results of serum CEA, serum CA72-4, and serum CA19-9 values, as well as the results of contrast-enhanced computed tomography scans of the abdomen and chest, lymph node ultrasound, craniocerebral enhanced magnetic resonance imaging, emission computed tomography or positron emission tomography-computed tomography were collected to carry out posttreatment assessments.

Efficacy and safety evaluation. Clinical efficacy was classified into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) based on the Response Evaluation Criteria in Solid Tumors. The objective response rate (ORR) included the rates of CR and PR. The disease control rate (DCR) included the rates of CR, PR, and SD. The overall survival (OS) duration was calculated as the interval from the day colorectal cancer was diagnosed to the end of follow-up or death. The progression-free survival (PFS) duration was calculated as the interval from the day treatment began to the end of follow-up or relapse. Adverse effects were evaluated as grade I–IV based on the Common Toxicity Criteria Version 3.0 of the National Cancer Institute.

Statistical analysis. Differences in qualitative data between the 3 groups were assessed by the chi-square test. Survival time was analyzed with the Kaplan-Meier method, and survival differences were analyzed by the log-rank test. Differences were regarded as meaningful when the p-value was less than 0.05. All data analysis was performed using the SPSS 21.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics. The clinical characteristics of the cases in the three groups are provided in Table 1. These characteristics, including sex, age, ECOG score, metastasis,

Table 1. Clinical characteristics of the patients.

Groups		Group A (n=35)	Group B (n=35)	Group C (n=35)	p-value
Sex n/%	Male	16/45.71	16/45.71	18/51.43	0.716
	Female	19/54.29	19/54.29	17/48.57	
Age (y) n%	≥60	11/31.43	13/37.14	11/31.43	0.581
	<60	24/68.57	22/62.86	24/68.57	
ECOG score n/%	0	0	0	0	0.371
	1	18/51.43	19/54.29	16/45.71	
	2	9/25.71	9/25.71	13/37.14	
	3	8/22.86	7/20.00	6/17.15	
Metastasis n/%	Pulmonary metastasis	21/65.63	26/74.29	19/54.29	0.091
	Bony metastasis	14/40.00	17/48.57	15/42.86	0.426
	Brain metastasis	6/17.14	7/20.00	7/20.00	0.823
	Hepatic metastasis	29/82.86	30/85.71	29/82.86	0.800
Receipt of antiangiogenic drugs n/%	Yes	19/54.29	21/60	17/48.57	0.294
	No	16/45.71	14/40	18/51.43	
Receipt of radiotherapy n/%	Yes	16/45.71	18/51.43	20/57.14	0.244
	No	19/54.29	17/48.57	15/42.86	
Receipt of surgery n/%	Yes	11/31.43	13/37.14	9/25.71	0.297
	No	24/68.57	22/62.86	26/74.29	
Receipt of TACE n/%	Yes	24/68.57	25/71.43	22/62.86	0.453
	No	11/31.43	10/28.57	13/37.14	

and receipt of antiangiogenic drugs (bevacizumab or cetuximab), TACE (transhepatic arterial chemoembolization), radiotherapy, or surgery, were not significantly different among the three groups (p>0.05).

Clinical efficiency. The rates of CR, PR, SD, and PD in the three groups were significantly different (p<0.001). All patients in the three groups did not achieve CR. The rates of PR and SD in group B (14.29% and 71.42%, respectively) were significantly higher than those in group A (0% and 40.00%, respectively). The rate of PD in group B (14.29%) was less than that in group A (60.00%). There was no significant difference in the rates of PR, SD, and PD between group B (14.29%, 71.42%, and 14.29%, respectively) and group C (20.00%, 65.71%, and 24.29%, respectively; p=0.539). The ORR and DCR in group B (14.29% and 85.71%, respectively) were higher than those in group A (0% and 40.00%, respectively). The ORRs of group B and group C were 14.29% and 20.00%, respectively. Group B and group C had the same DCR, 85.71%. Data on clinical efficiency were detailed in Table 2.

Comparison of PFS and OS among the three groups. The mean PFS values of group B (3.46 months) and group C (3.33 months) were longer than that of group A (2.25 months) (χ^2=84.255, p<0.001) and the mean values of group B and group C were similar (χ^2=0.884, p=0.347). The survival curves of the PFS for the three groups are shown in Figure 1. The survival curves of the PFS for group B and group C are detailed in Figure 2.

Table 2. Clinical efficacy of the three therapies.

Groups	Group A (n=35)	Group B (n=35)	Group C (n=35)	p-value
CR n/%	0	0	0	
PR n/%	0	5/14.29	7/20.00	
SD n/%	14/40.00	25/71.42	23/65.71	p<0.001
PD n/%	21/60.00	5/14.29	5/14.29	
p-value		p=0.539		

The mean OS of group B was 9.22 months, longer than that of group A 6.95 months (χ^2=38.837, p<0.001). The mean OS values of group B (9.22 months) and group C (9.38 months) were not significantly different (χ^2=0.456, p=0.499). The survival curves of OS for the three groups are shown in Figure 3. Survival curves of OS for group B and group C are detailed in Figure 4.

Comparison of adverse effects. The incidences of adverse effects, including proteinuria, hand-foot skin reaction (HFSR), myelosuppression, and gastrointestinal reaction were similar between group B and group C (p=0.173, 0.188, 1.00, and 0.154, respectively). It is worth noting that proteinuria and HFSR appeared in only group B and group C. Myelosuppression and gastrointestinal reaction were more common in group A than in group B and group C (p<0.001). The incidences of various adverse reactions in the three groups are detailed in Table 3.
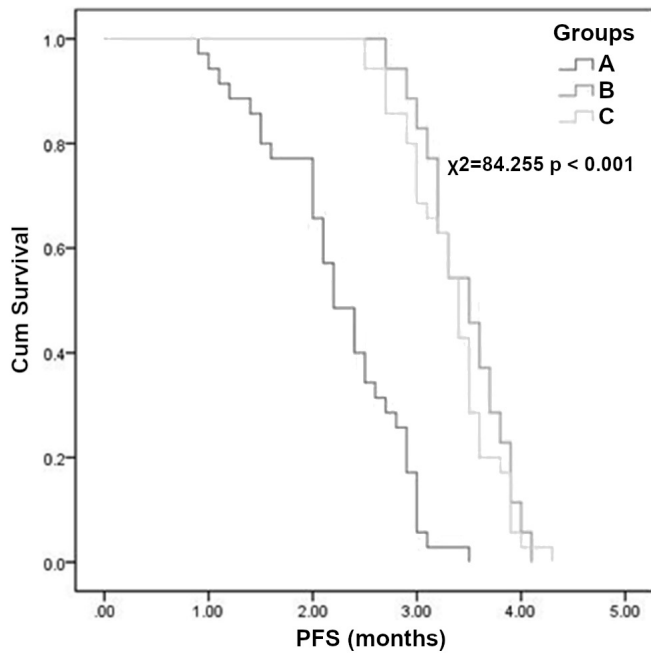
Figure 1. Survival curves of PFS for the three groups: group A) third-line chemotherapy only; group B) anlotinib; group C) fruquintinib or regorafenib. The mean PFS values of group B (3.46 months) and group C (3.33 months) were longer than that of group A (2.25 months) (χ^2=84.255, p<0.001).
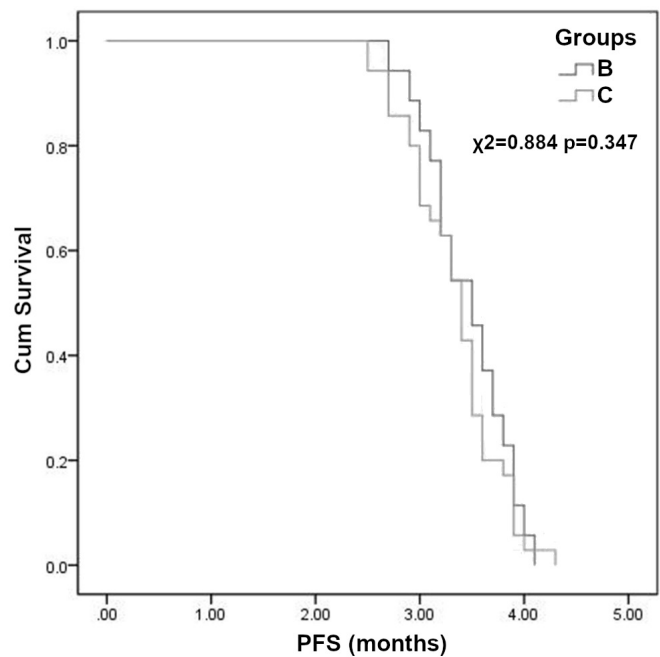

Figure 2. Survival curves of PFS for group B and group C: group B) anlotinib; group C) fruquintinib or regorafenib. The PFS values of group B (3.46 months) and group C (3.33 months) were similar (χ^2=0.884, p=0.347).
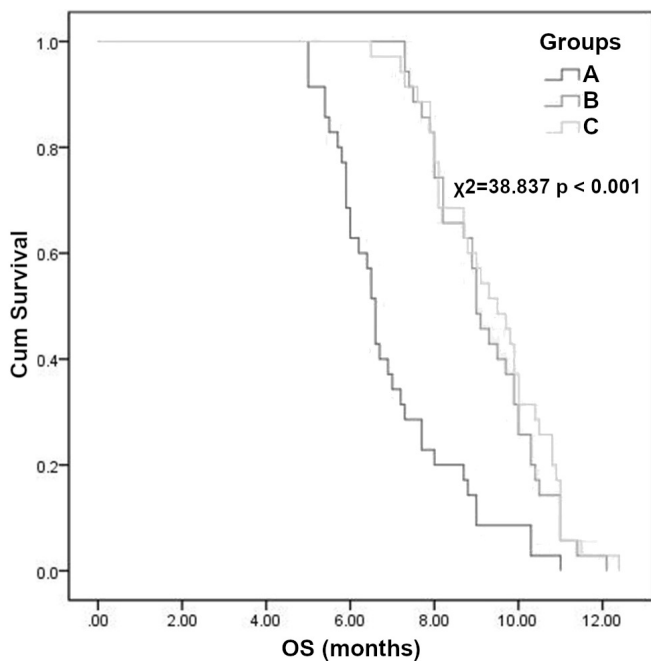

Figure 3. Survival curves of OS for the three groups: group A) third-line chemotherapy only; group B: anlotinib; group C: fruquintinib or regorafenib. The mean OS values of group B (9.22 months) and group C (9.38 months) were longer than that of group A (6.95 months) (χ^2=38.837, p<0.001).
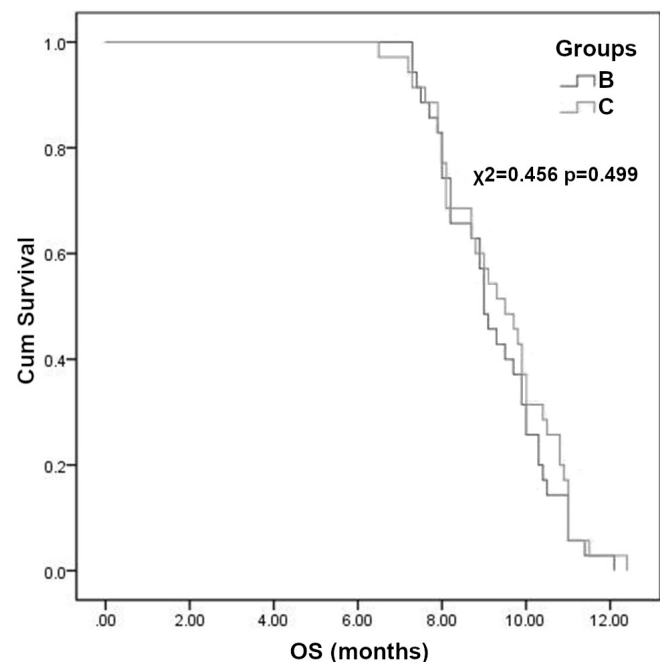

Figure 4. Survival curves of OS for group B and group C: group B) anlotinib; group C) fruquintinib or regorafenib. The mean OS values of group B (9.22 months) and group C (9.38 months) were not significantly different (χ^2=0.456, p=0.499).

Table 3. Comparison of adverse effects among the three groups.

Adverse effects		Group A (n=35)	Group B (n=35)	Group C (n=35)	p1*
HFSR, n/%	Yes	0/0.00	6/17.14	8/22.86	p<0.001
	No	35/100.00	29/82.86	27/77.14	
p2*			p=0.188		
Proteinuria, n/%	Yes	0/0.00	5/14.29	7/20.00	p<0.001
	No	35/100.00	30/85.71	28/80.00	
p2*			p=0.173		
Gastrointestinal reaction, n/%	Yes	16/45.71	4/11.43	6/17.14	p<0.001
	No	19/54.29	31/88.57	29/82.86	
p2*			p=0.154		
Myelosuppression, n/%	Yes	11/31.43	1/2.86	1/2.86	p<0.001
	No	24/68.57	34/97.14	34/97.14	
p2*			p=1.000		

*p1: p-value of the three groups; p2: p-value of group B vs. group C.

Discussion

Anlotinib can inhibit both tumor angiogenesis and tumor cell proliferation by targeting VEGFR1, VEGFR2/KDR, VEGFR3, c-Kit, PDGFR-α, and fibroblast growth factor receptors (FGFR1, FGFR2, and FGFR3). Moreover, it can inhibit more targets than other RTK inhibitors, including sorafenib, sunitinib, and pazopanib [29, 30]. Therefore, it has recently become a hot topic of research.

Anlotinib has obtained good clinical results in advanced NSCLC [22, 23], advanced STS [24, 25], advanced MTC [26, 27], and mRCC [28]. A phase III trial named ALTER-0303 enrolled 437 advanced NSCLC patients who progressed after at least two lines of prior treatments. The ORR and DCR were improved in the anlotinib group compared with the placebo group (ORR 9.18% vs. 0.7%, p<0.0001; DCR 80.95% vs. 37.06%, p<0.0001). The median PFS and OS of the anlotinib group were prolonged compared with those of the placebo group (PFS 5.37 vs. 1.40 months, p<0.0001; OS 9.63 vs. 6.30 months, p<0.0001) [23]. Therefore, anlotinib was approved by the China Food and Drug Administration for third-line treatment or beyond in advanced NSCLC on May 8, 2018, in China [31]. Stacchiotti et al. conducted a phase IIB study that enrolled 233 advanced STS patients who were treatment-intolerant or progressed on anthracycline-based chemotherapy [25]. The results showed that the ORR and DCR in the anlotinib group were significantly higher than those in the control group (ORR 10.13% vs. 1.33%, p=0.0145; DCR 55.7% vs. 22.67%, p<0.0001). The median PFS of anlotinib was significantly improved relative to that of the control (6.27 months vs. 1.47 months, p<0.0001) [32]. The clinical study results were presented in the oral report section at the American Society of Clinical Oncology annual meeting. Zhou et al. conducted a multicenter randomized phase II trial that enrolled 133 mRCC patients (93 treated with anlotinib and 40 treated with sunitinib) [27]. The results showed that the anlotinib and sunitinib groups had similar PFS values (11.3 vs. 11.0 months, p=0.30), ORR (24.4% vs. 23.3%) and 6-week DCRs (97.8% vs. 93.0%, p=0.33) [27]. A phase II trial enrolled 58 patients with advanced or relapsed MTC who could not receive radical surgery and treated them with anlotinib. The average PFS was 12.8 months (median PFS not reached), the overall ORR was 48.28%, and the DCRs at weeks 24 and 48 were 92.16% and 84.53%, respectively [28].

However, there has been no clinical study exploring the efficiency and safety of anlotinib as a treatment for mCRC. There are limited methods for treating mCRC, especially for patients who progress after at least two lines of prior treatments. Therefore, it is of great significance to find effective third-line targeted drugs for mCRC patients. In this retrospective clinical analysis, one hundred and five mCRC patients who failed at least two lines of chemotherapy were divided into three groups based on their third-line therapeutic regimen. Their basic clinical characteristics were very similar. After follow-up and analysis, none of the patients in the three groups achieved a CR. The PR and SD rates of group B (14.29% and 71.42%, respectively) were significantly higher than those of group A (0% and 40.00%, respectively). The rate of PD in group B (14.29%) was less than that in group A (60.00%). There was no significant difference in the rates of PR, SD, or PD between group B (14.29%, 71.42%, and 14.29%, respectively) and group C (20.00%, 65.71%, and 24.29%, respectively) (p=0.539). The ORR and DCR of group B (14.29% and 85.71%, respectively) were higher than those of group A (0% and 40.00%, respectively). The ORRs of group B and group C were 14.29% and 20.00%, respectively. Group B and group C had the same DCR, 85.71%. The mean PFS values of group B (3.46 months) and group C (3.33 months) were longer than that of group A (2.25 months) (χ^2=84.255, p<0.001) and the mean PFS values of group B and group C were similar (χ^2=0.884, p=0.347). The mean OS of group B was 9.22 months, longer than that of group A (6.95 months) (χ^2=38.837, p<0.001). The mean OS values of group B (9.22 months) and group C (9.38 months)

were not significantly different (χ^2=0.456, p=0.499). The incidences of adverse effects, including proteinuria, hand-foot skin reaction (HFSR), myelosuppression, and gastrointestinal reaction were similar between group B and group C (p=0.173, 0.188, 1.00, and 0.154, respectively). It is worth noting that proteinuria and HFSR appeared in only group B and group C. Myelosuppression and gastrointestinal reaction were more common in group A than in group B and group C (p<0.001).

The reason why anlotinib can obtain good clinical efficiency in various cancers, including mCRC, may be closely related to its molecular mechanism. Preclinical studies on endothelial cells provided enough evidence to prove that cell migration and the formation of capillary-like tubes induced by EGF/PDGF-BB/FGF-2 can be inhibited by anlotinib. The possible mechanisms may be that anlotinib inhibits the activation of VEGFR2, PDGFRβ, and FGFR1, as well as downstream ERK signaling. In addition, anlotinib can bind to the ATP-binding pocket of the VEGFR2 tyrosine kinase and inhibit VEGFR2 with high selectivity (IC50 < 1 nM), thereby inhibiting VEGF-stimulated proliferation of human umbilical vein endothelial cells (HUVECs). Moreover, HUVEC migration, tube formation, and microvessel growth *in vitro* were suppressed and vascular density was reduced *in vivo* by anlotinib [33]. In summary, anlotinib obtained good clinical efficiency in various cancers by effectively inhibiting cell proliferation and migration signaling pathways via multiple targets.

In this retrospective clinical analysis, anlotinib had an outstanding clinical effect in the treatment of mCRC patients who progressed after at least two lines of prior treatments in terms of the ORR, DCR, and survival time. This means that anlotinib may become another effective targeted drug for mCRC. Of course, these results need to be supported by clinical trials with larger sample sizes.

In conclusion, anlotinib, as a newly approved orally administrative small-molecule RTK inhibitor, has better clinical efficiency as a third-line treatment than chemotherapy for metastatic colorectal cancer patients who failed at least two lines of chemotherapy. In comparison to that of other targeted drugs, such as regorafenib or fruquintinib, the clinical effect is comparable, and the adverse reactions are similar and tolerable.

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