

A Retrospective Cohort Study Evaluates Clinical Value of Anlotinib in Persistent, Metastatic, or Recurrent Cervical Cancer After Failure of First-Line Therapy

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Background: Anlotinib is an oral anti-angiogenesis inhibitor targeting vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors, fibroblast growth factor receptors, etc., and its clinical value in cervical cancer is rarely reported. We designed a retrospective study to evaluate the efficacy and safety of anlotinib in patients with persistent, metastatic, or recurrent cervical cancer who have failed first-line therapy, and compare the efficacy of anlotinib with that of apatinib which targets only VEGFR2 and has shown efficacy in recent studies.

Methods: Fifty-two patients with persistent, metastatic, or recurrent cervical cancer who failed first-line therapy and administered anlotinib or apatinib as monotherapy or combination with chemo-, radio- or immunotherapy were included in this study. Among the 52 patients, 20 patients who received anlotinib from January 2019 to August 2020 were defined as anlotinib group, whereas 32 patients who received apatinib from our previous study were selected as apatinib group. The safety, objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were reviewed and recorded.

Results: The ORR and DCR in patients receiving anlotinib were 25% and 80%, respectively. The median PFS and OS in anlotinib group were significantly longer than those in apatinib group, respectively (PFS: 5 months vs 3 months, $p=0.015$; OS: 10 months vs 5 months, $p=0.008$). Moreover, the patients treated with anlotinib had better survival with a significantly lower cumulative incidence of cancer-related death than those treated with apatinib (HR=0.31, 95% CI: 0.13–0.77, $p=0.012$). The most common adverse effects in the patients treated with anlotinib were hypertension (20%), fatigue (20%), and nausea (15%). No drug-related death occurred.

Conclusion: Anlotinib showed beneficial efficacy and safety and can be a treatment option for patients with persistent, metastatic, or recurrent cervical cancer who have failed the first-line therapy.

Keywords: angiogenesis, anlotinib, cervical cancer, efficacy, safety, retrospective study

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Introduction

Cervical cancer is still the most common cancer in the female reproductive system.¹ After standardized treatment, the average 5-year overall survival (OS) of patients with stage I–III cervical cancer is 45%. However, the 5-year OS is only 15% after the disease becomes persistent, recurrent, or metastatic due to ineffective strategies.² Therefore, it is urgent to explore effective treatment strategies for persistent, recurrent, or metastatic cervical cancer.

Anti-angiogenesis targeted therapy has become one of the treatment strategies for many tumors. Cervical cancer is no exception. The GOG240 study showed that compared to paclitaxel plus cisplatin alone, paclitaxel and cisplatin combined with bevacizumab, which targeted vascular endothelial growth factor (VEGF), can improve the response rates (RR) (from 36% to 48%), progression-free survival (PFS) (from 5.9 to 8.2 months) and OS (from 13.3 to 17 months).³ Similarly, other anti-angiogenesis drugs, apatinib, cediranib, and pazopanib, have shown effective and low toxicity in advanced and recurrent cervical cancer.⁴ However, recent studies have found that when tumor tissue is hypoxic, it can produce three signal molecules: VEGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). When VEGF-related signaling pathways are blocked, tumor tissues can up-regulate the expression of other cytokines through escape and bypass activation (such as FGF and PDGF) to maintain their nutritional supply.⁵ It suggests that simultaneous blocking of the downstream signal pathways mediated by VEGF-receptor (VEGFR), FGF-receptor (FGFR), and PDGF-receptor (PDGFR) could more comprehensively inhibit tumor angiogenesis, thereby exerting a favorable antitumor effect.

Anlotinib is an anti-angiogenic drug that can fully inhibit VEGFR, PDGFR, and FGFR. It can inhibit tumor cell proliferation and migration by inhibiting stem cell factor receptor (c-Kit) and cellular-mesenchymal epithelial transition factor (c-Met).⁶ Due to the unique cyclopropyl structure of the drug, the half-maximal inhibitory concentration (IC₅₀) of anlotinib at each target is low, and the activity is vigorous; more importantly, the main target of anlotinib is tyrosine kinase (TK).⁷ These characteristics enable anlotinib to inhibit angiogenesis and tumor growth simultaneously, and it is more delayed than other single-target anti-angiogenic drugs to develop drug resistance and has fewer side effects. It has been approved by the China State Food and Drug Administration (CSFDA) for locally advanced or metastatic non-small cell lung cancer patients who have progressed or relapsed after receiving at least two types of systemic chemotherapy in the past.⁸ Moreover, studies have reported that the drug has shown promising efficacy and safety in esophageal squamous cell carcinoma,⁹ soft tissue sarcoma,¹⁰ medullary thyroid carcinoma,¹¹ ovarian cancer,¹² and other tumors.¹³ However, no clinical studies have reported the efficacy and safety of anlotinib in patients with cervical cancer,

let alone assessing whether the efficacy of anlotinib is better than single anti-VEGF drugs.

Apatinib is an oral anti-angiogenesis drug that only targets VEGFR2. Recently, others and our previous studies have shown that apatinib has efficacy and safety in patients with cervical cancer.^{4,14–20} To explore the efficacy of anlotinib in persistent, recurrent, or metastatic cervical cancer and determine whether the efficacy of anlotinib is superior to single anti-VEGF drugs, we selected patients who received apatinib in our previous studies as a control group. Therefore, this study performed a retrospective study not only to evaluate the efficacy and safety of anlotinib in persistent, recurrent, or metastatic cervical cancer, but also to compare the difference in overall response rate (ORR), disease control rate (DCR), PFS, and OS between anlotinib group and apatinib group.

Materials and Methods

Patient Eligibility

This retrospective study was performed to analyze clinical data on patients with persistent, metastatic, or recurrent cervical cancer who were treated with anlotinib or apatinib and met the inclusion and exclusion criteria in Zhongnan Hospital of Wuhan University.

All patients in this study had undergone one comprehensive treatment and signed informed consent to take anlotinib or apatinib. Persistent and recurrent cervical cancer that failed the first-line therapy was defined as disease progression following initial surgery, chemo-, or radiotherapy in or after 6 months, respectively, and then the disease progressed again after receiving systemic treatment. Metastatic cervical cancer that failed the first-line therapy was defined as the disease progression that appeared after systemic therapy in the patients with stage IVB (according to the International Federation of Gynecology and Obstetrics (FIGO) staging) cervical cancer. Patients had at least one measurable lesion and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. Before treatment, patients were confirmed not to be treated with anti-angiogenesis drugs and no risk of bleeding and/or have grade II coronary heart disease, uncontrollable high blood pressure, arrhythmia, cardiac insufficiency, nausea and swallow, chronic diarrhea, and intestinal obstruction. Patients who have not finished at least one cycle of anlotinib or apatinib treatment were also excluded from this study. The patients in anlotinib group were included in our hospital from January 2019 to August 2020. The patients in apatinib

group were selected from our previous retrospective cohort study.¹⁴

Treatment and Dose Modification

Anlotinib was initially taken 12mg orally every day for 14 days and then stopped for 7 days (21 days as a cycle). The daily dosage was reduced from 12mg to 10mg when the patients could not tolerate it. If the patients were still intolerant, the daily dosage was adjusted from 10mg to 8mg. After radiotherapy, patients suspended anlotinib treatment. After chemotherapy, patients were continually administered anlotinib till disease progression or unacceptable toxicity. The treatment and dose modification of apatinib were described in our previous study.¹⁴

Efficacy and Safety Assessments

All patients in anlotinib group were followed up until June 2021. According to the solid tumor efficacy evaluation standard (RECIST 1.1), tumor response included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Overall response rate (ORR) was calculated by the ratio of CR plus PR (CR+PR) to the total number of patients. Disease control rate (DCR) was calculated by the percentage of CR, PR plus SD (CR+PR+SD) to the total number of patients. Progression-free survival (PFS) was defined from initiating anlotinib treatment to clinical or radiographic progression or death. Overall survival (OS) was measured from firstly anlotinib therapy to death or last contact. Based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE 5.0), the toxicity was recorded from patients' medical history, telephone follow-up, or laboratory examination results. The records of efficacy in patients treated with apatinib were described in our previous study.¹⁴

Statistical Analysis

Statistical analysis was performed using SPSS version 25 (IBM, NC, USA). Median (95% confidence interval) or the number of patients (percentage) were used to describe patients' survival and clinical characteristics. The Wilcoxon or Kruskal–Wallis *H*-test was applied to analyze the efficacy difference between two or three groups. Kaplan–Meier method and the Log rank test were used to compare the survival of patients between different treatment groups. The multivariate Cox regression analysis was used to evaluate the independent prognostic factors. The difference was defined as statistically significant when $p < 0.05$ (two-tails).

Results

Patient Characteristics

A total of 52 patients with persistent, recurrent, or metastatic cervical cancer who had failed first-line therapy were included in this retrospective study. Among the 52 patients, 20 patients who received anlotinib from January 2019 to August 2020 were defined as anlotinib group, whereas 32 patients who received apatinib from our previous study were selected as apatinib group. All patients in this study have previously received surgery and/or chemotherapy and radiotherapy; no bevacizumab was received before. In anlotinib group, 80% of patients experienced disease progression, and 70% of patients died. The baseline characteristics were summarized in Table 1. There were no differences between anlotinib and apatinib groups among patients in different age groups ($p=0.855$), different administration strategies ($p=0.072$), different initial conditions ($p=1.000$), and different prior treatments ($p=1.000$). But the patients in different treatment lines ($p=0.034$) and pathological types ($p=0.033$) showed differences between the anlotinib and apatinib groups.

Table 1 The Baseline Characteristics in This Study

Characteristics	Anlotinib n=20(%)	Apatinib n=32(%)	p-value
Age			
<50	7(35%)	12(37.5%)	0.855
≥50	13(65%)	20(62.5%)	
Pathological types			
SCC	13(65%)	29(90.6%)	0.033
AC and others	7(35%)	3(9.4%)	
Treatment lines			
Second	6(30%)	18(56.3%)	0.034
Third	9(45%)	13(40.5%)	
Further	5(25%)	1(3.1%)	
Administration strategies			
Monotherapy	4(20%)	19(59.4%)	0.072
Combined with chemotherapy	9(45%)	9(28.1%)	
Combined with radiotherapy	2(10%)	4(12.5%)	
Combined with immunotherapy	5(25%)	0(0.0%)	
Initial conditions			
Recurrent	18(90%)	29(90.6%)	1.000
Metastatic	2(10%)	3(9.4%)	
Prior treatments			
Surgery, radiotherapy, and chemotherapy	11(55%)	18(56.3%)	1.000
Radiotherapy and chemotherapy	9(45%)	14(43.7%)	

Notes: The bold value indicates p-value is statistically significant.

Abbreviations: SCC, squamous cervical carcinoma; AC, cervical adenocarcinoma.

Efficacy

In anlotinib group, at the end of follow-up time on June 30, 2021, no patient occurred CR, 5 patients showed PR, 11 patients had SD, 4 patients had PD. The ORR and DCR were 25% and 80%, respectively (Table 2). There was no statistical difference in the efficacy of anlotinib among patients of different age groups ($p=0.157$), different pathological types ($p=0.877$), different treatment lines of anlotinib ($p=0.402$), different anlotinib administration strategies ($p=0.610$), and different initial conditions ($p=0.290$) (Table 3). In apatinib group, no patient occurred CR, 7 patients showed PR, 17 patients had SD, 8 patients had PD. The ORR and DCR were 21.88% and 75%, respectively (Table 2). When we compared the tumor response between anlotinib and apatinib groups, no statistically significant had been found ($p=0.678$) (Table 2). These results suggested that similar to apatinib, the anlotinib was also showed efficacy in patients with cervical cancer.

Survival Analysis

In anlotinib group, the median PFS and OS were 5.0 months (95% CI: 0–10.48) and 10.0 months (95% CI: 6.10–13.90), respectively (Table 4 and Figure 1). The 1-year survival rate was 43.7%. There were no differences of PFS and OS in patients of different age groups (PFS: $p=0.749$, OS: $p=0.976$), different pathological types (PFS: $p=0.299$, OS: $p=0.179$), different treatment lines of anlotinib (PFS: $p=0.286$, OS: $p=0.177$), and different initial conditions (PFS: $p=0.687$, OS: $p=0.586$), respectively (Table 4). But the differences of PFS and OS in patients with different anlotinib administration strategies were statistically significant (PFS: $p=0.0001$, OS: $p=0.030$) (Table 4). There were only 2 patients administrated anlotinib combined with radiotherapy. The overall survival

Table 2 The Difference of Tumor Response Between Anlotinib and Apatinib

Tumor Response	Anlotinib	Apatinib	p-value
CR	0	0	0.678
PR	5	7	
SD	11	17	
PD	4	8	
ORR ^a (%)	25%	21.88%	
DCR ^b (%)	80%	75%	

Notes: ^aORR, the ratio of the number of CR and PR (CR+PR) patients to the total number of patients; ^bDCR, the ratio of the number of CR, PR, and SD (CR+PR+SD) patients to the total number of patients.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; ORR, objective response rate.

Table 3 The Difference of Tumor Response Between Different Characteristics in Anlotinib Group

Characteristics	CR	PR	SD	PD	p-value
Total	0	5	11	4	
Age					
<50	0	1	3	3	0.157
≥50	0	4	8	1	
Pathological types					
SCC	0	3	8	2	0.877
AC and others	0	2	3	2	
Treatment lines					
Second	0	3	2	1	0.402
Third	0	2	5	2	
Further	0	0	4	1	
Administration strategies					
Monotherapy	0	1	2	1	0.610
Combined with chemotherapy	0	1	6	2	
Combined with radiotherapy	0	1	0	1	
Combined with immunotherapy	0	2	3	0	
Initial conditions					
Recurrent	0	5	9	3	0.290
Metastatic	0	0	2	1	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SCC, squamous cervical carcinoma; AC, cervical adenocarcinoma.

time for them was 4.5 and 6.0 months, respectively. Since only 1 of 5 patients in the group of anlotinib combined with immunotherapy have died, the median OS had not reached yet. The overall survival of the patient who was died in the group of anlotinib combined with immunotherapy was 8 months. At the end of follow-up time, the other 4 patients in the group of anlotinib combined with immunotherapy were still alive, and their OS was 11, 12, 12 and 20 months, respectively. As shown in Figure 2, the PFS and OS rate seemed the highest in patients administrated anlotinib combined with immunotherapy than those in other administration strategies. In contrast, the PFS and OS rate was the lowest in patients administrated anlotinib combined with radiotherapy. However, the association between different anlotinib administration strategies and prognosis in this study cannot be elucidated because of the small sample size and short follow-up time.

When we performed the Kaplan-Meier method and Log rank test to analyze the difference of PFS and OS between patients treated with anlotinib and apatinib, the results revealed that the median PFS and OS of patients treated with apatinib were 3 months (95% CI: 1.42–4.58 months)

Table 4 Univariable Analysis of PFS and OS in Anlotinib Group

Characteristics	mPFS in Months (95% CI)	p-value	mOS in Months (95% CI)	p-value
Total	5.0(0–10.48)		10(6.10–13.90)	
Age				
<50	3.5(0–7.35)	0.749	10(0–20.27)	0.976
≥50	6.5(2.39–10.61)		11.5(5.68–17.32)	
Pathological types				
SCC	7.5(0–16.31)	0.299	14(11.28–16.72)	0.179
AC and others	3.5(0–9.92)		8(5.66–10.34)	
Line of anlotinib				
Second	12.75(0–25.85)	0.286	14(2.55–25.45)	0.177
Third	3.5(1.31–5.70)		8(2.89–13.11)	
Further	7.5(0–16.09)		10(4.63–15.37)	
Administration strategies				
Monotherapy	7.5(0–17.50)	0.0001	11.5(0.23–22.77)	0.030
Combined with chemotherapy	3.5(2.04–4.96)		9.5(5.12–13.88)	
Combined with radiotherapy	0.5		4.5	
Combined with immunotherapy	Not reached		Not reached	
Initial conditions				
Recurrent	6.5(1.12–11.88)	0.687	11.5(8.45–14.56)	0.586
Metastatic	5(0–12.20)		8(4.80–11.20)	

Note: The bold value indicates p-value is statistically significant.

Abbreviations: mPFS, median progression-free survival; mOS, median overall survival; SCC, squamous cervical carcinoma; AC, cervical adenocarcinoma.

and 5 months (95% CI: 3.49–6.51 months), respectively, which were significantly shorter than those of patients treated with anlotinib (PFS, $p=0.015$; OS, $p=0.008$) (Figure 3). The multivariate analysis showed that treated with anlotinib was an independent protecting factor only in OS (HR=0.31, 95% CI 0.13–0.77, $p=0.012$), not in PFS (HR=0.47, 95% CI

0.21–1.09, $p=0.080$) (Figure 4). In addition, third-line treatment with anlotinib or apatinib was an independent risk factor for both PFS (HR=2.04, 95% CI 1.02–4.07, $p=0.044$) and OS (HR=2.16, 95% CI 1.01–4.63, $p=0.047$) (Figure 4). These results showed that the efficacy of anlotinib may be superior to that of apatinib.

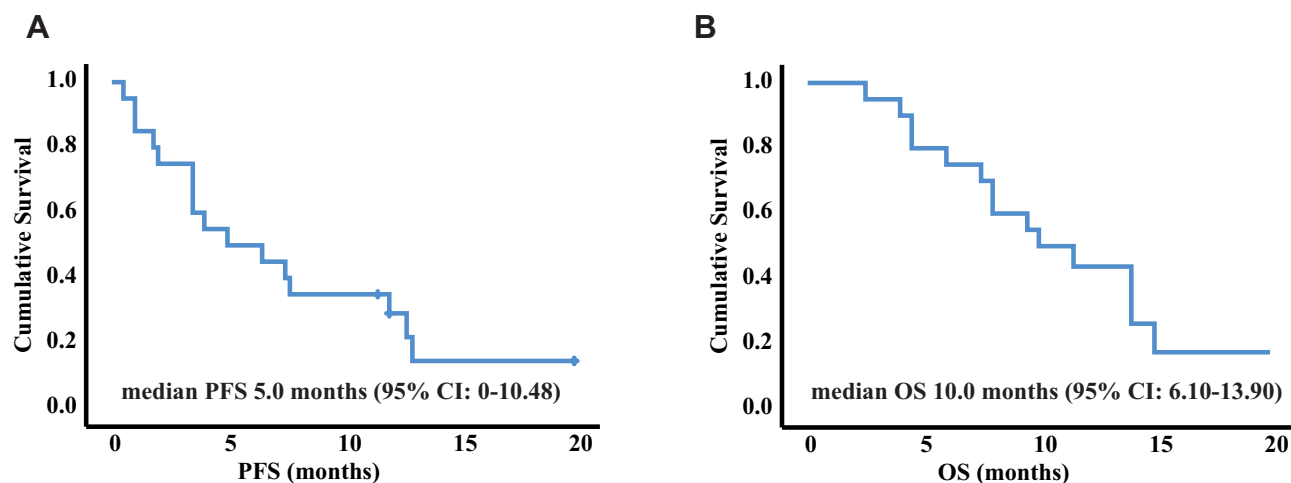


Figure 1 The Kaplan-Meier analysis and Log rank test assess the PFS (A) and OS (B) of patients in anlotinib group.

Abbreviations: PFS, progression-free survival; OS, overall survival.

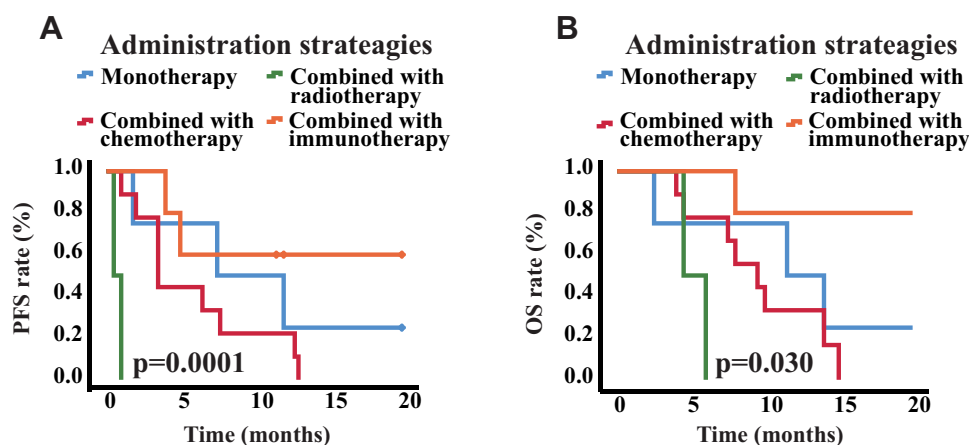


Figure 2 (A) The survival curve of PFS in patients after administrated anlotinib with different strategies. (B) The survival curve of OS in patients after administrated anlotinib with different strategies.

Abbreviations: PFS, progression-free survival; OS, overall survival.

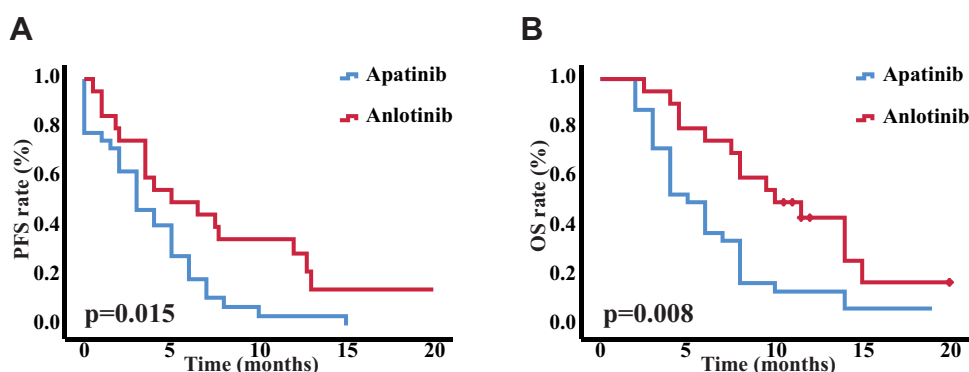


Figure 3 The Kaplan-Meier analysis and Log rank test assess the difference of PFS (A) and OS (B) between the patients treated with anlotinib and those treated with apatinib.

Abbreviations: PFS, progression-free survival; OS, overall survival.

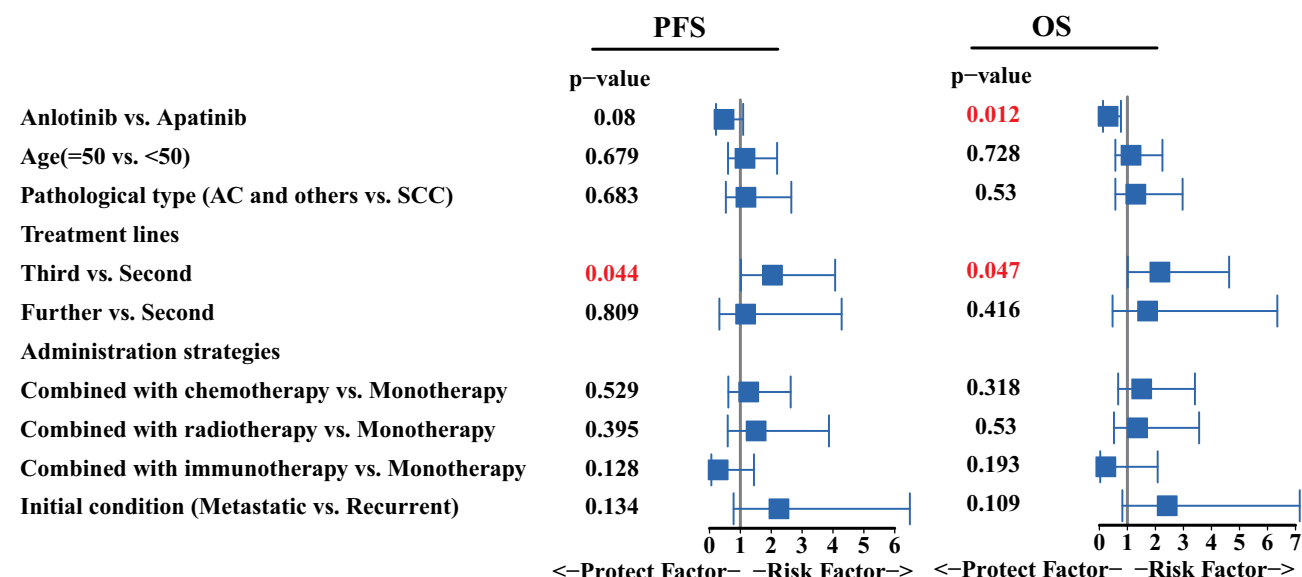


Figure 4 The multivariate analysis of PFS and OS in this study.

Abbreviations: PFS, progression-free survival; OS, overall survival; SCC, squamous cervical carcinoma; AC, cervical adenocarcinoma.

Adverse Effects (AEs)

In this study, 11 people experienced adverse action, including 2 with the hand-foot syndrome, 3 with nausea, 4 with hypertension, 4 with fatigue, 2 with neutropenia, 1 with proteinuria, 1 with vomiting, 1 with mucositis oral, and 1 with diarrhea (Table 5). Two patients had Grade 3 adverse events of hypertension, and their blood pressure could be controlled after taking antihypertensive drugs. One patient had grade 3 neutropenia. After stopping anlotinib and receiving granulocyte colony-stimulating factor, it can be restored to the normal level. When received anlotinib again, the dose will be reduced from 12mg to 10mg. One patient developed severe fatigue and mucositis oral, respectively, which resolved after stopping anlotinib. The total incidence of grade 3–4 adverse events was 30%. The remaining toxicities were grade 1 to 2.

Discussion

In this study, we demonstrate for the first time that anlotinib showed efficacy and safety in patients with persistent, metastatic, or recurrent cervical cancer who have failed the first-line therapy. Furthermore, this study revealed that compared the efficacy of patients treated with anlotinib to the patients treated with apatinib, the patients treated with anlotinib was an independent protecting factor in OS.

In 1971, Professor Judah Folkman published a new theory that “tumor growth depends on angiogenesis” and proposed an “anti-angiogenesis” tumor treatment strategy.²¹ Since then, tumor-targeted anti-angiogenesis therapy has become one of the treatment methods for

many tumors. In cervical cancer, the results of GOG240 make bevacizumab combined with paclitaxel and cisplatin become the standard first-line treatment for recurrent and metastatic cervical cancer. However, due to the lack of effective treatment methods, the National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with recurrent and metastatic cervical cancer who have failed first-line treatment can participate in clinical trials to seek new effective remedies, which is essential to improve the overall survival rate of cervical cancer. Studies have shown that alternative angiogenic pathway activated was one of the reasons for anti-VEGF resistance.⁵ The alternative angiogenic pathway includes FGF, PDGF, angiopoietin 1, etc.²² Blocking VEGF, FGF and PDGF at the same time may more comprehensively inhibit tumor angiogenesis than just anti-VEGF, thereby exerting an antitumor effect.

Some drugs targets both VEGF, FGF, and PDGF have been studied in cervical cancer.²³ Pazopanib targets the VEGFR, PDGFR, FGFR, and c-Kit. Studies have explored the efficacy of pazopanib monotherapy in recurrent and metastatic cervical cancer.²⁴ The results showed that the ORR, DCR, median PFS, and OS of pazopanib were 9.5%, 52.7%, 4.5, and 12.4 months, respectively.²⁴ Sunitinib, similar to pazopanib, could target VEGFR, PDGFR, and c-Kit.²⁵ But studies showed that sunitinib is highly toxic without any survival benefit in both PFS and OS.²⁵ In this study, anlotinib was used to treat recurrent metastatic cervical cancer that failed the first-line treatment. The ORR and DCR were 25% and 80%, respectively, which were higher than the results of pazopanib. These may be

Table 5 Adverse Effects (AEs) in Anlotinib Group

Adverse Event	Total n (%)	No. of Patients			
		Grade 1	Grade 2	Grade 3	Grade 4
Hand-foot syndrome	2(10%)	2	0	0	0
Nausea	3(15%)	3	0	0	0
Hypertension	4(20%)	0	2	2	0
Fatigue	4(20%)	3	0	1	0
Hemorrhage	0(0%)	0	0	0	0
Neutropenia	2(10%)	1	0	1	0
Canker sore	0(0%)	0	0	0	0
Proteinuria	1(5%)	0	0	1	0
Vomiting	1(5%)	1	0	0	0
Mucositis oral	1(5%)	0	0	1	0
Diarrhea	1(5%)	1	0	0	0
None	9(45%)	0	0	0	0

because anlotinib targets not just VEGFR, PDGFR, FGFR, and c-Kit, but also c-Met. Some studies have found that c-Met can be activated through negative feedback exerted by VEGF.²⁶ So inhibiting c-Met is a method to overcome resistance to anti-VEGF therapy.⁵ However, the median PFS and OS in this study were 5 and 10 months, respectively, which were identical to those in the pazopanib study. Without treatment, the 1-year survival rate for patients with persistent, metastatic, or recurrent cervical cancer is less than 20%.²⁷ In this study, the 1-year survival rate was 43.7%, indicating that anlotinib may have efficacy in patients with cervical cancer.

In 2020, Xu et al have reported results from a Phase II study of sintilimab plus anlotinib for patients with persistent, recurrent, or metastatic cervical cancer in ESMO.²⁸ The ORR and DCR were 70.6% and 100%, respectively. The median PFS had not reached. Similarly, the ORR and DCR of patients who were treated anlotinib combined with immunotherapy in our study were 40% and 100%, respectively. Although the median OS of patients treated with anlotinib and immunotherapy had not reached, the survival curve in [Figure 1B](#) demonstrated that the patients treated with anlotinib and immunotherapy live a relatively longer life than others. Anlotinib has been shown in several studies to alleviate immunosuppression by enhancing T cell, NK cell, and APC cell infiltration and reducing the formation and aggregation of immunosuppressive Treg cells and TAM cells.^{29,30} Thus, anlotinib combined with immunotherapy might be an effective therapy in cervical cancer.

When we compared the efficacy of anlotinib in this study to that of apatinib reported in our previous study,¹⁴ the results showed that the patients treated with anlotinib had a relatively longer PFS and OS than those treated with apatinib. Then, the multivariate analysis showed that compared with the second-line treatment, treated anlotinib or apatinib as third-line was an independent risk factor in PFS and OS, which meant that patients who received anlotinib or apatinib as second-line therapy had a better prognosis than those treated as third-line therapy. Although the baseline of treatment lines is inconsistent between patients in anlotinib and apatinib group, [Table 1](#) has shown that the composition ratio of patients treated with second-line therapy in anlotinib group was significantly lower than that in apatinib group. It suggested that patients in apatinib group should have better survival than those in anlotinib group. However, in fact, treated with anlotinib was an independent protecting factor in OS. These results implied that

the multi-targeted anti-angiogenic drug might have a better effect than single targeted anti-angiogenic drugs.

Similarly, the GOG-0227C study used bevacizumab as a single agent to treat recurrent and metastatic cervical cancer.³¹ Among the enrolled patients, 73.9% were first-line drugs, and 26.1% were second-line drugs.³¹ The median PFS and OS of the study were 3.4 months and 7.3 months, respectively, which were lower than the results of this study.³¹ These results again support that anlotinib, a multi-targeted anti-angiogenic drug, has better effects than a single anti-angiogenic drug targeting vascular endothelial growth factors.

The common side effects in this study are similar to those of other anti-angiogenic drugs, including hand-foot syndrome, nausea, hypertension, fatigue, and neutropenia. High blood pressure, fatigue, and neutropenia had grade 3–4 adverse events, and their incidence was 10%, 5%, and 5%, respectively. RTOG0417 is a study to explore the efficacy and safety of bevacizumab combined with radiotherapy in advanced cervical cancer.³² The incidence of grade 3 and grade 4 bone marrow suppression in this study was 22.45% and 6.12%, which were higher than ours.³² GOG240 is a study comparing the efficacy of bevacizumab combined with chemotherapy and chemotherapy alone.³ 6% of patients treated with bevacizumab combined with chemotherapy in GOG240 experienced grade 3 fistula adverse events, which was higher than that in the chemotherapy alone group.³ In this study, anlotinib did not have this adverse event regardless of single-agent, combined chemotherapy, combined radiotherapy. It can be seen that the adverse reactions of anlotinib in the treatment of cervical cancer are relatively low, and the side effects of the drug can be tolerated regardless of single-drug or combined use.

In conclusion, anlotinib has a certain effect in patients with persistent, recurrent, or metastatic cervical cancer who have failed first-line treatment, and the side effects are tolerable. The efficacy of anlotinib may be much better than the single anti-VEGF drugs. However, as the small sample size in this study and the self-limitation of retrospective study, further prospective clinical trials are needed to confirm our findings and establish the most suitable treatment strategy of anlotinib to benefit patients.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics Statement

This study followed the principles of the Helsinki Declaration and was approved by the Ethics Committee of Zhongnan Hospital, Wuhan University, Hubei, China (Permit Number:2021030). All patients signed informed consent in this study.

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Disclosure

The authors report no conflicts of interest in this work.

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