

Feasibility and Safety of Anlotinib Monotherapy for Patients with Previously Treated Advanced Esophageal Squamous Cell Carcinoma: A Real-World Exploratory Study

Song Zhang, Xin Wang, Hao Gu, Jun-Qi Liu

Department of Radiation Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, 450052, People's Republic of China

Correspondence: Jun-Qi Liu, Department of Radiation Oncology, The First Affiliated Hospital of Zhengzhou University, No. 1 Jian-She East Road, Zhengzhou, Henan, 450052, People's Republic of China, Tel +86 13938550770, Email fccliujq@zzu.edu.cn

Objective: This study was to investigate the feasibility and safety of anlotinib monotherapy for patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC) retrospectively.

Methods: This study was designed as a real-world study. A total of 83 patients with advanced or metastatic ESCC who received anlotinib monotherapy were included. Demographic characteristics of the patients, efficacy data of the treatment and adverse reactions during the treatment were documented and analyzed through the electronic medical record system in the hospital. All the patients were followed up regularly. The primary endpoint of this study was progression-free survival (PFS), secondary endpoints were objective response rate (ORR), disease control rate (DCR), overall survival (OS), safety profile and PFS analysis according to adverse reactions.

Results: A total of 83 patients with ESCC who received anlotinib monotherapy were included. Partial response was observed in 7 patients, stable disease was noted in 51 patients and progressive disease was found in 25 patients, which yielded an ORR of 8.4% (95% CI: 3.5–16.6%), and a DCR of 69.9% (95% CI: 58.8–79.5%). Furthermore, the median PFS of the 83 patients with advanced ESCC was 3.3 months (95% CI: 2.20–4.40) and the median OS was 7.8 months (95% CI: 5.40–10.20). Common adverse reactions among the 83 patients were hypertension (51.8%), fatigue (48.2%), weight loss (41.0%), diarrhea (34.9) and hand-foot syndrome (30.1%). Correlation analysis between hypertension status and PFS suggested that PFS of the patients with hypertension was longer than that of those with non-hypertension (median PFS: 4.5 vs 3.0 months, $P = 0.019$).

Conclusion: Anlotinib monotherapy demonstrated promising efficacy and tolerable toxicity for patients with previously treated advanced or metastatic ESCC. Hypertension that occurs during anlotinib administration might be used as a potential biomarker to predict PFS of patients with ESCC. The conclusion should be confirmed in prospective clinical trials subsequently.

Keywords: esophageal squamous cell carcinoma, anlotinib, efficacy, safety, hypertension, biomarker

Introduction

Esophageal cancer was reported to be one of the most common gastrointestinal tumors and the eighth most common malignancy annually all over the world.¹ There were approximately 324,000 new cases and 301,000 deaths of esophageal cancer in China recorded currently.² To our knowledge, a great discrepancy is observed regarding the histological type of esophageal cancer between the East and West nations, which highlights that esophageal adenocarcinoma is the predominant disease in western countries, while approximately 95% of esophageal cancers in China are esophageal squamous cell carcinoma (ESCC).³ Given that the etiology and the molecular characteristics are different, the treatment of esophageal cancer in China has its own methods and the therapeutic strategies for ESCC should be developed separately from those for esophageal adenocarcinoma in order to optimize the patient outcomes.⁴ Most patients with ESCC are diagnosed with locally advanced or metastatic disease initially.⁵ Cisplatin combined with 5-FU or paclitaxel chemotherapy were the standard of care as first-line therapy for the patients over the past decades. First-line regimen of

cisplatin plus 5-FU for patients with ESCC could achieve an objective response rate (ORR) of 33%, a median progression-free survival (PFS) of 5.5 months and overall survival (OS) of 10 months,⁶ and the regimen of cisplatin plus paclitaxel might yield an ORR of 43%, a median PFS of 6 months and OS of 12 months.⁷ Irinotecan, docetaxel or paclitaxel were all available as second-line chemotherapy for advanced ESCC over the past decades clinically,⁸ which yielded an ORR of 7.5%, a median PFS of 3 months and median OS of approximately 7.1 months.

To our knowledge, immune checkpoint inhibitors initially demonstrated promising antitumor activity and tolerable toxicity as second-line or further-line therapy for patients with advanced or metastatic ESCC. Pembrolizumab, nivolumab and PD-1 blockades in China all provided patients with survival benefits when used in a second-line setting.⁹ Subsequently, a great breakthrough was also observed after the adoption of PD-1 blockades in combination with chemotherapy. Indeed pembrolizumab, nivolumab and camrelizumab plus chemotherapy, respectively, as first-line treatment have brought varying degrees of improvement of prognosis in patients with advanced ESCC.¹⁰ Unfortunately, therapeutic options with tolerable safety profile for patients with advanced ESCC when failed after the treatment of front-line PD-1 blockades and systemic chemotherapy are still limited and efficacious regimens are needed urgently.

It should be noted that, as an oral, antiangiogenic multi-targeted tyrosine kinase inhibitor (TKI) that selectively inhibits VEGFR2/3, PDGFR α/β , FGFR1-4 and c-Kit, anlotinib had become a new standard of care as third-line therapy for patients with non-small cell lung cancer (NSCLC) in China since 2018.¹¹ Furthermore, anlotinib demonstrated a promising efficacy as second-line treatment for patients with advanced ESCC with an ORR of 7.34%, median PFS of 3.02 months and median OS of 6.11 months according to the ALTER1102 phase II clinical trial.¹² Consequently, anlotinib monotherapy might be a promising therapeutic option for patients with ESCC who failed after the previous treatment of systemic chemotherapy.

Additionally, the overall response of antiangiogenic targeted drug monotherapy for advanced ESCC has also been disappointing, with the ORR ranging from 7–10% clinically.¹³ Therefore, it is necessary to explore the potential biomarkers that might predict the response and prognosis of patients with advanced ESCC who received anlotinib monotherapy. Interestingly, a previous retrospective study investigated the feasibility of anlotinib monotherapy among elderly patients with previously treated extensive-stage SCLC.¹⁴ The conclusion indicated that hypertension and hand-foot syndrome induced by the administration of anlotinib might be used as potential biomarkers to predict the PFS of patients with SCLC. However, the clinical significance of hypertension among patients with advanced ESCC who received anlotinib administration remains unknown.

Consequently, the present study was to investigate the feasibility and safety profile of anlotinib monotherapy for patients with advanced or metastatic ESCC. Furthermore, correlation analysis between hypertension induced by anlotinib treatment and PFS was performed simultaneously.

Patients and Methods

Research Design and Eligibility Criteria

Given that anlotinib has been approved in China for over three years, a considerable number of patients with advanced or metastatic ESCC have been treated with anlotinib monotherapy in clinical practice, so this study was designed retrospectively. Therefore, patients with advanced ESCC who had been treated with previous systemic chemotherapy in the Department of Oncology and Department of Radiation Oncology of the first affiliated hospital of Zhengzhou University from July 2018 to November 2021 were included in this study consecutively. The main inclusion criteria were: (1) histologically confirmed esophageal squamous cell carcinoma with advanced or metastatic disease; (2) eastern cooperative oncology group (ECOG) performance status (PS) of 0–2 score; (3) age of ≥ 18 years; (4) patients were treated with previous systemic chemotherapy and had disease progression or intolerant of the corresponding regimen, including concurrent chemoradiotherapy or systemic chemotherapy; (5) patients were treated with anlotinib monotherapy in clinical practice; (6) patients had at least one measurable target lesion to present the drug response according to the response evaluation criteria in solid tumors (RECIST 1.1). Additionally, the main exclusion criteria included: (1) patients were presence of symptomatic or active brain metastases, those who had stable brain metastasis were permitted to be

included; (2) patients who had active hemorrhage at the primary lesions over the previous two months, given that anlotinib might contribute to bleeding; (3) patients with dysphagia in view of the fact that anlotinib was administered orally. However, patients with dysphagia were also eligible if an alternative feeding route was available; (4) patients were concomitant with another cancer or serious diseases that might compromise the survival of the patients; (5) efficacy assessment data of the patients were not available. Ultimately, a total of 83 patients were included in our study, and the study profile is illustrated in Figure 1. The primary endpoint of this study was PFS, secondary endpoints were ORR, DCR, OS and safety profile. Furthermore, the exploratory endpoint was the association analysis between hypertension and PFS. This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. Each patient was provided with written informed consent according to the recommendations of the Declaration of Helsinki.

Therapeutic Regimens and Assessment Protocol Regarding Efficacy and Safety

All the patients included in this study were treated with anlotinib monotherapy. Local treatment (mainly radiotherapy) for non-target lesions was also permitted. Anlotinib monotherapy was administered orally at an initial dosage of 12 mg or 10 mg (determined by the investigator) daily with warm water for two weeks and discontinued for one week, every three weeks as one therapeutic cycle. The treatment was continued until progression or intolerable adverse reactions. Additionally, dosage reduction was adjusted according to the tolerance of the patients.

Treatment response was evaluated using RECIST version 1.1 criteria according to the judgement of investigators. Target lesion in chest was assessed with computed tomography (CT), target lesions in other positions were assessed using CT or magnetic resonance imaging (MRI) for each patient before and after the administration of anlotinib. Target lesions were assessed every two cycles or when it was necessary in clinic (clinical symptoms of the patients were getting worse). The calculation of ORR and DCR in this study was analyzed based on the results of the best overall response evaluated during the treatment of anlotinib.¹⁵ Additionally, safety profile was assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria.

Additionally, in the analysis of the prognostic significance of adverse reactions, this study mainly performed an association analysis between the occurrence of hypertension and PFS. It should be noted that hypertension was defined as

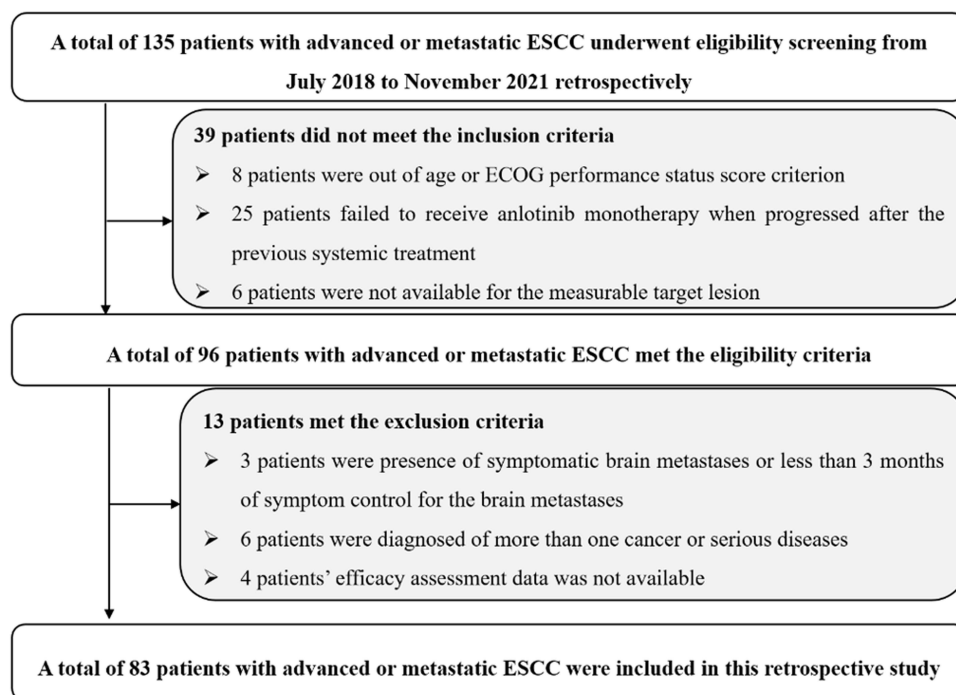


Figure 1 The study profile of the retrospective research regarding anlotinib monotherapy for patients with previously treated advanced or metastatic esophageal squamous cell carcinoma.

either new-onset hypertension or worsening grade (based on CTCAE v4.03) from baseline in patients with a history of hypertension using actual blood pressure measurements. For preexisting hypertension, any increase in drug dosage or initiation of a new antihypertensive agent was denoted as grade 3 hypertension.

Furthermore, overall survival was also measured in this study. Given that this study was designed as a retrospective study, clinical demographic characteristics, adverse reactions and status of disease progression of each patient were collected through the electronic medical record system when the patients underwent hospitalization. The subsequent follow-up was mainly carried out by telephone. Patients were followed up once a month and the death status was mainly inquired. The data cut-off date of this study was January 5, 2022.

Statistical Analysis

ORR was defined as the proportion of complete response (CR) and partial response (PR) among all the included patients. DCR was defined as the proportion of CR and PR and stable disease (SD) among all the patients included. All the statistical analysis was carried out using SPSS version 25.0. Difference of variables according to hypertension status was analyzed using chi-square test and the Mann–Whitney U non-parametric test, respectively. Quantitative variables and qualitative variables were presented as median (range) and number of patients (percentage), respectively. PFS and OS were defined according to a previous study.¹⁴ Survival curves were drawn using Stata 14.0 software to present PFS and OS. The survival difference was analyzed using Log rank test. Multivariate Cox regression analysis was adopted for PFS including the variables that were significant in univariate analysis. $P < 0.05$ was considered significant.

Results

Baseline Characteristics of the 83 Patients with ESCC

Baseline characteristics of the 83 patients with previously treated advanced or metastatic ESCC are shown in Table 1. Obviously, those included in this study were the patients with advanced or metastatic ESCC clinically. Regarding the hypertension analysis, as shown in Table 1, 43 patients had hypertension and 40 were non-hypertensive. It should be noted that all the baseline characteristics of patients with hypertension were balanced with those of patients with non-hypertension ($P > 0.05$).

Efficacy in the 83 Patients with ESCC Who Received Anlotinib Monotherapy

All the 83 patients with advanced or metastatic ESCC who received anlotinib monotherapy from July 2018 to November 2021 were available for the efficacy evaluation. The results of each radiographic assessment using CT or MRI were collected and recorded. Efficacy assessment was based on the best overall response during the therapeutic process. As a result, partial response (PR) was observed in 7 patients, stable disease (SD) was noted in 51 patients and progressive disease (PD) was found in 25 patients, which yielded an ORR of 8.4% (95% confidence interval (CI): 3.5–16.6%), and DCR was 69.9% (95% CI: 58.8–79.5%). Specifically, the waterfall plot for the best percentage change in target lesion of the 83 patients with ESCC who received anlotinib monotherapy is illustrated in Figure 2. This shows that a certain number of patients benefited from anlotinib monotherapy administration, whose target lesions shrank significantly. The chest CT scan of the target lesions in esophagus and lung sites of a PR patient before and after the administration of anlotinib monotherapy is illustrated in Figure 3. The target lesion shrank dramatically after anlotinib administration. The imaging result suggested that this patient benefited significantly from the treatment of anlotinib monotherapy.

Prognosis of the 83 Patients with ESCC Who Received Anlotinib Monotherapy

The data cut-off date of this study was January 5, 2022. With regard to the follow-up data, the median follow-up duration of the 83 patients with ESCC from the date of anlotinib administration to the date of data cut-off was 7.3 months (follow-up range: 0.3–26 months). In terms of the PFS data, a total of 65 disease progression or death events were observed at the date of data cut-off, which yielded a maturity for PFS data of 78.3%. As shown in Figure 4, the median PFS of the 83 patients with advanced or metastatic ESCC who received anlotinib monotherapy was 3.3 months (95% CI: 2.20–4.40).

Table I Demographic and Clinical Characteristics of the 83 Patients with Advanced or Metastatic ESCC According to Hypertension Status

Characteristics	Total Patients (N = 83, %)	Hypertension Status		χ^2	P
		Hypertension (N = 43)	Non-Hypertension (N = 40)		
Age (years) Median (range)	66 (21–81)	66 (21–79)	66 (25–81)	NA	0.531
Gender					
Male	62 (74.7)	33 (76.7)	29 (72.5)	0.1	0.6
Female	21 (25.3)	10 (23.3)	11 (27.5)	98	57
ECOG PS score					
0–1	51 (61.4)	27 (62.8)	24 (60.0)	0.0	0.7
2	32 (38.6)	16 (37.2)	16 (40.0)	68	94
Distant metastasis					
Yes	76 (91.6)	39 (90.7)	37 (92.5)	0.0	0.7
No	7 (8.4)	4 (9.3)	3 (7.5)	87	68
Previous surgical treatment					
Yes	34 (41.0)	18 (41.9)	16 (40.0)	0.0	0.8
No	49 (59.0)	25 (58.1)	24 (60.0)	30	63
Lines of anlotinib treatment					
Second-line	9 (10.8)	5 (11.6)	4 (10.0)	0.0	0.8
Third-line or further-line	74 (89.2)	38 (88.4)	36 (90.0)	57	12
Previous targeted drugs therapy					
Yes	16 (19.3)	8 (18.6)	8 (20.0)	0.0	0.8
No	67 (80.7)	35 (81.4)	32 (80.0)	26	72
Previous PD-1 blockades therapy					
Yes	20 (24.1)	11 (25.6)	9 (22.5)	0.1	0.7
No	63 (75.9)	32 (74.4)	31 (77.5)	08	43
Number of metastatic sites					
≤2	56 (67.5)	28 (65.1)	28 (70.0)	0.2	0.6
>2	27 (32.5)	15 (34.9)	12 (30.0)	25	35
Initial dosage of anlotinib (mg)					
12	59 (71.1)	31 (72.1)	28 (70.0)	0.0	0.8
10	24 (28.9)	12 (27.9)	12 (30.0)	44	34

Abbreviations: ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NA, not available; PD-1, programmed death ligand 1.

Additionally, it was noteworthy that the 6-month PFS and 12-month PFS rate was 34.8% (95% CI: 24.4–45.5%) and 13.1% (95% CI: 5.3–24.6%), respectively.

Furthermore, the association between PFS and baseline characteristic subgroups was performed subsequently. The median PFS and 95% CI according to baseline characteristic subgroups are shown in Table 2. Obviously, patients benefited from anlotinib monotherapy uniformly regardless of the baseline characteristic subgroups. However, it is noteworthy that patients with ECOG performance status 0–1 score had a significantly better PFS than those with 2 score in univariate analysis (median PFS: 4.5 vs 2.5 months, $P = 0.013$). Interestingly, patients who received PD-1 blockades administration previously had a trend for superior PFS compared with those who failed to receive PD-1

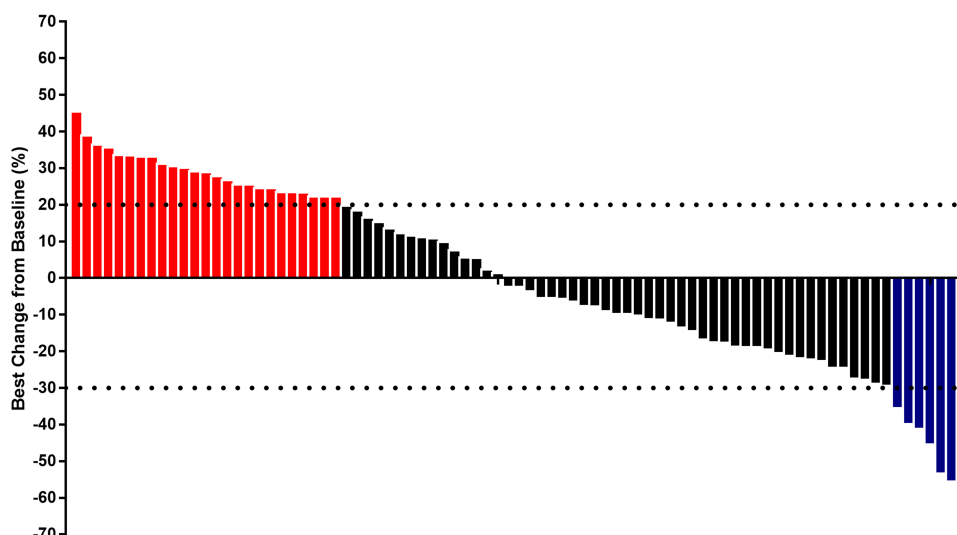


Figure 2 Waterfall plot for the best percentage change in target lesion of the 83 patients with advanced or metastatic esophageal squamous cell carcinoma who received anlotinib monotherapy (blue columns represent PR, black columns represent SD and red columns represent PD in the best overall response).

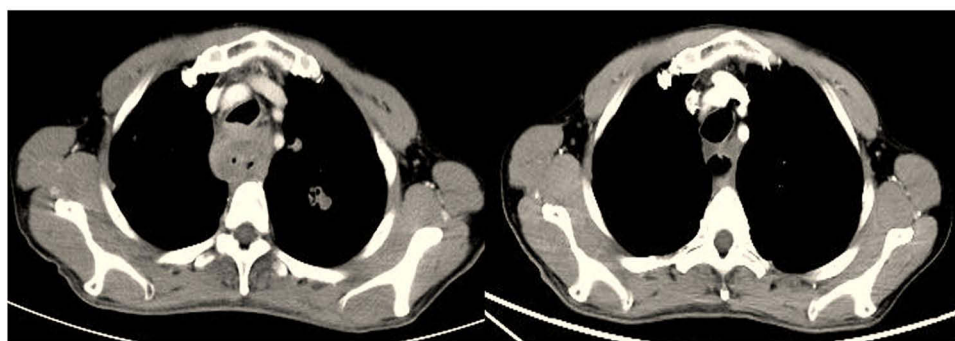


Figure 3 The CT scan results of the changes for target lesions in esophagus and lung sites of one patient with esophageal squamous cell carcinoma before and after the administration of anlotinib monotherapy.

blockades treatment, although the difference was not statistically significant (median PFS: 4.2 vs 3.0 months, $P = 0.103$).

Furthermore, given that the follow-up duration of this study was long enough, OS analysis was also carried out simultaneously. Accordingly, a total of 56 death events were observed at the date of data cut-off, which resulted in a maturity for OS data of 67.5%. As illustrated in [Figure 5](#), the median OS of the 83 patients with advanced or metastatic ESCC who received anlotinib administration was 7.8 months (95% CI: 5.40–10.20). Additionally, the 12-month OS and 24-month OS rate were 40.9% (95% CI: 29.8–51.6%) and 21.3% (95% CI: 11.1–33.7%), respectively.

Safety Profile

The safety profile of anlotinib was safe and controllable and no grade 5 adverse reactions were detected during anlotinib administration. The maximum adverse reactions among the 83 patients with ESCC that occurred during anlotinib administration were collected and analyzed in this study. Treatment-related adverse reactions were observed in 75 patients (90.4%) among the 83 patients with ESCC; grade 3–4 adverse reactions were recorded in 29 patients (34.9%).

Specifically, the relatively common adverse reactions are shown in [Table 3](#). Furthermore, the most common grade 3–4 adverse reactions were hypertension (15.7%), fatigue (6.0%), weight loss (4.8%), hand-foot syndrome (3.6%), diarrhea (2.4%), nausea and vomiting (2.4%), hematological toxicity (2.4%) and AST/ALT elevation (1.2%).

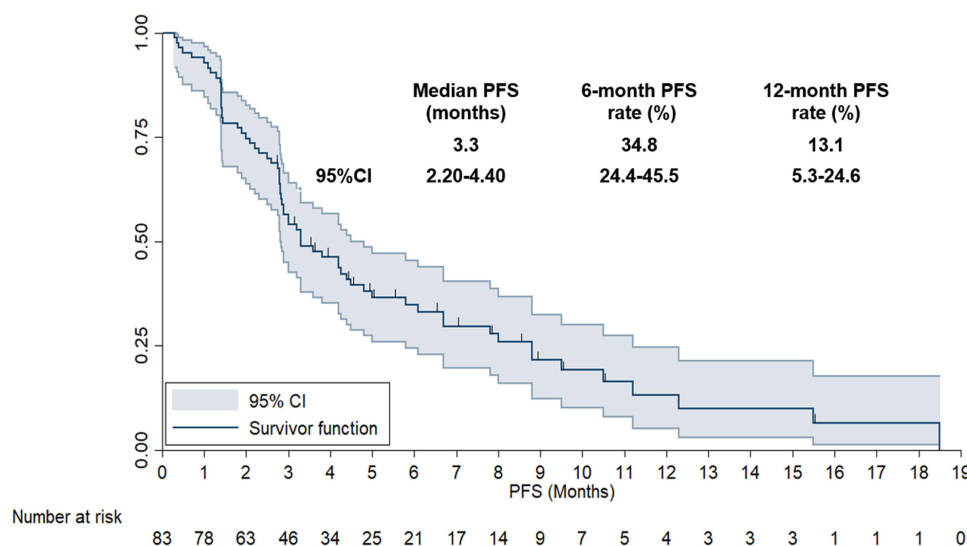


Figure 4 The progression-free survival curve of the 83 patients with advanced or metastatic esophageal squamous cell carcinoma who received anlotinib monotherapy.

Additionally, of the 83 patients who received anlotinib monotherapy, a total of 10 patients (12.0%) underwent dose reduction due to adverse reactions such as hypertension, fatigue and diarrhea. A total of 4 patients (4.8%) experienced treatment interruption owing to hypertension (2 cases), AST/ALT elevation (1 case) and hematological toxicity (1 case).

Correlation Analysis Between PFS and Hypertension Status

Given that hypertension was the most common adverse reaction and easy to monitor, the prognostic association analysis was mainly focused on hypertension in this study. As shown in Table 3, a total of 43 patients were observed with hypertension during anlotinib administration. Accordingly, the PFS of the 83 patients with advanced or metastatic ESCC according to hypertension status is illustrated in Figure 6. The median PFS of patients with hypertension and non-hypertension was 4.5 months (95% CI: 0.00–9.05) and 3.0 months (95% CI: 2.38–3.62), respectively, the difference was statistically significant ($\chi^2 = 5.51$, $P = 0.019$).

Furthermore, Cox regression analysis for PFS was introduced with ECOG performance status which were significant in univariate analysis to adjust the confounding factors, as illustrated in Table 4. After the multivariate adjustment, hypertension status was still confirmed to be an independent factor for PFS (Hazard Ratio (HR) = 0.67, $P = 0.029$). Additionally, ECOG performance status score was also an independent factor for PFS after multivariate adjustment (HR = 0.56, $P = 0.021$).

Discussion

Our study investigated the feasibility and safety profile of 83 patients with previously treated advanced or metastatic ESCC who received anlotinib monotherapy in real-world practice. The results suggested that anlotinib monotherapy was of preliminary therapeutic significance and acceptable toxicity as further-line treatment for patients with advanced or metastatic ESCC. Simultaneously, the correlation analysis indicated that the hypertension induced by anlotinib monotherapy might be used as a potential biomarker to predict superior PFS for patients with ESCC.

Esophageal cancer was one of the most common malignant tumors in digestive system with substantial heterogeneity. Recent years have witnessed a gradual rising trend regarding the prevalence of esophageal cancer in the Chinese population.⁹ To our knowledge, esophageal cancer has strong Chinese characteristics and ESCC was the most common cancer category in China. As a result, considerable studies in Western countries focusing on esophageal adenocarcinoma were not applicable for Chinese ESCC patients.¹⁶ However, relatively limited research progress was observed regarding the targeted drugs in the field of advanced or metastatic ESCC recently, and the classical platinum combined with 5-FU or paclitaxel regimens had been used in clinical practice over the past two decades.¹⁷ Engagingly, breakthrough research

Table 2 Univariate Analysis Between PFS of the 83 Patients with ESCC and Baseline Characteristic Subgroups

Characteristic	N	Median PFS (Months)	95% CI	P
Age (Years)				
≥66	45	3.2	2.15–4.25	0.618
<66	38	3.3	2.31–4.29	
Gender				
Male	62	3.0	2.06–3.94	0.536
Female	21	3.8	2.58–5.02	
ECOG PS score				
0–I	51	4.5	0.00–9.05	0.013
2	32	2.5	1.95–3.05	
Distant metastasis				
Yes	76	3.3	2.12–4.48	0.438
No	7	3.6	2.45–4.75	
Previous surgical treatment				
Yes	34	3.6	2.33–4.87	0.525
No	49	3.0	1.98–4.02	
Lines of anlotinib treatment				
Second-line	9	3.8	2.68–4.92	0.625
Third-line or further-line	74	3.3	2.14–4.46	
Previous targeted drugs therapy				
Yes	16	3.6	2.57–4.63	0.436
No	67	3.3	2.08–4.52	
Previous PD-1 blockades therapy				
Yes	20	4.2	2.07–6.33	0.103
No	63	3.0	1.95–4.05	
Number of metastatic sites				
≤2	56	4.3	3.15–5.45	0.371
>2	27	3.3	2.17–4.43	
Initial dosage of anlotinib (mg)				
12	59	3.8	2.65–4.95	0.205
10	24	3.0	1.89–4.11	

Abbreviations: ESCC, esophageal squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group; PS, performance status; NA, not available; PD-1, programmed death ligand 1.

progress had been achieved regarding immune checkpoint inhibitors (mainly PD-1 blockades) in advanced ESCC since 2019. Pembrolizumab and nivolumab had exhibited promising clinical activity as second-line therapy for patients with advanced ESCC according to the Keynote-181 and Attraction-3 clinical trials.^{8,18} However, the two studies only recruited a small number of Chinese patients, thus the therapeutic value was relatively limited in China. Camrelizumab (a PD-1 blockade in China) demonstrated compelling efficacy as second-line therapy for patients with ESCC in China according to the ESCORT clinical trial.¹⁹ Recently, consecutive clinical trials confirmed that PD-1 blockades combined with chemotherapy demonstrated great breakthrough for patients with advanced ESCC and could be the standard of care as first-line therapy for patients with ESCC, according to the Keynote 590, Checkmate 648 and ESCORT-1st clinical trials.^{20–22} Still, overall, therapeutic options with tolerable safety profile for patients with advanced ESCC who failed after the treatment of PD-1-based regimens and systemic chemotherapy were scanty and efficacious regimens were needed urgently.

The ORR and DCR of the 83 patients with advanced or metastatic ESCC who received anlotinib monotherapy were 8.4% and 69.9%, respectively, and the median PFS of the present study was 3.3 months, which are basically consistent with the results in the ALTER1102 clinical trial initiated by Professor Huang et al.¹² A total of 109 patients with previously treated ESCC in the ALTER1102 trial were recruited and treated with anlotinib or placebo randomly. Patients

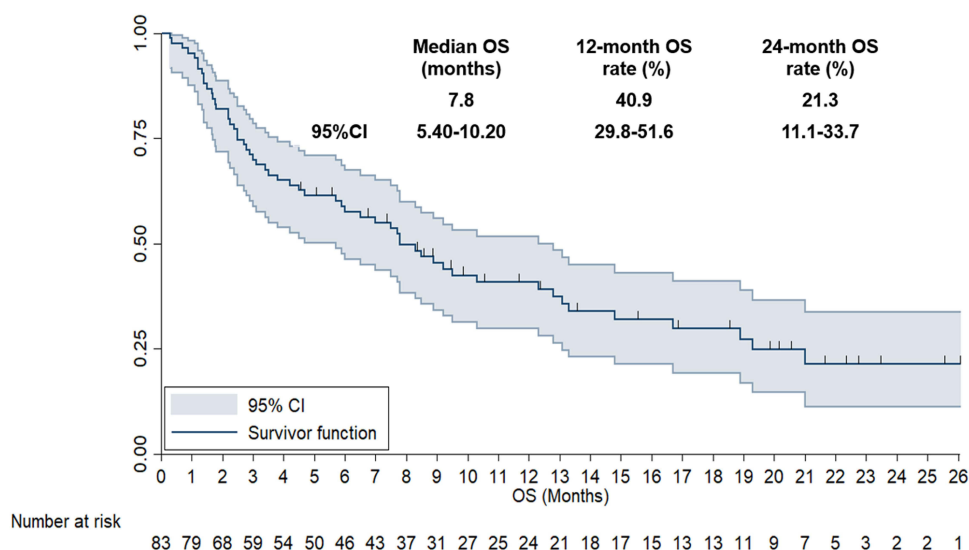


Figure 5 The overall survival curve of the 83 patients with advanced or metastatic esophageal squamous cell carcinoma who received anlotinib monotherapy.

who received anlotinib monotherapy achieved an ORR of 9.1%, DCR of 77.3% and median PFS of 3.02 months. The efficacy data in the ALTER1102 trial were comparable with those in our study. However, it should be noted that the proportion of patients who received anlotinib as second-line treatment was lower than that in the ALTER1102 trial (10.8% vs 36%), which suggested that anlotinib monotherapy was usually administered for patients with treatment-refractory ESCC in real-world clinical practice.²³ Additionally, a recent phase II study initiated by Chu et al. investigated the efficacy and safety of apatinib (another antiangiogenic TKI, similar to anlotinib) monotherapy among patients with advanced ESCC.²⁴ A total of 40 patients with chemotherapy-refractory ESCC who received apatinib monotherapy were included, which yielded an ORR of 7.5%, a DCR of 65.0%, a median PFS of 3.8 months and median OS of 5.8 months. These findings were basically consistent with those of our study. The above data suggested that antiangiogenic TKI demonstrated preliminary effectiveness for patients with previously treated advanced ESCC. Furthermore, association analysis between PFS and baseline characteristic subgroups was also implemented in our study. Apparently, it seemed that patients benefited from anlotinib monotherapy uniformly regardless of the baseline characteristic subgroups, which was in concert with a previous retrospective study regarding anlotinib monotherapy for patients with advanced NSCLC.²⁵

Table 3 Safety Profile of the 83 Patients with ESCC Who Received Anlotinib Monotherapy

Adverse Reactions	Total (N, %)	Grade 1–2 (N, %)	Grade 3–4 (N, %)
Any grade adverse reactions	75 (90.4)		29 (34.9)
Hypertension	43 (51.8)	30 (36.1)	13 (15.7)
Fatigue	40 (48.2)	35 (42.2)	5 (6.0)
Weight loss	34 (41.0)	30 (36.1)	4 (4.8)
Diarrhea	29 (34.9)	27 (32.5)	2 (2.4)
Hand-foot syndrome	25 (30.1)	22 (26.5)	3 (3.6)
AST/ALT elevation	19 (22.9)	17 (20.5)	1 (1.2)
Nausea and vomiting	18 (21.7)	16 (19.3)	2 (2.4)
Proteinuria	15 (18.1)	15 (18.1)	0 (0.0)
Dysphonia	12 (14.4)	12 (14.4)	0 (0.0)
Hematological toxicity	9 (10.8)	7 (8.4)	2 (2.4)
Stomatitis	6 (7.2)	6 (7.2)	0 (0.0)
Hemorrhage	4 (4.8)	4 (4.8)	0 (0.0)

Abbreviations: ESCC, esophageal squamous cell carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

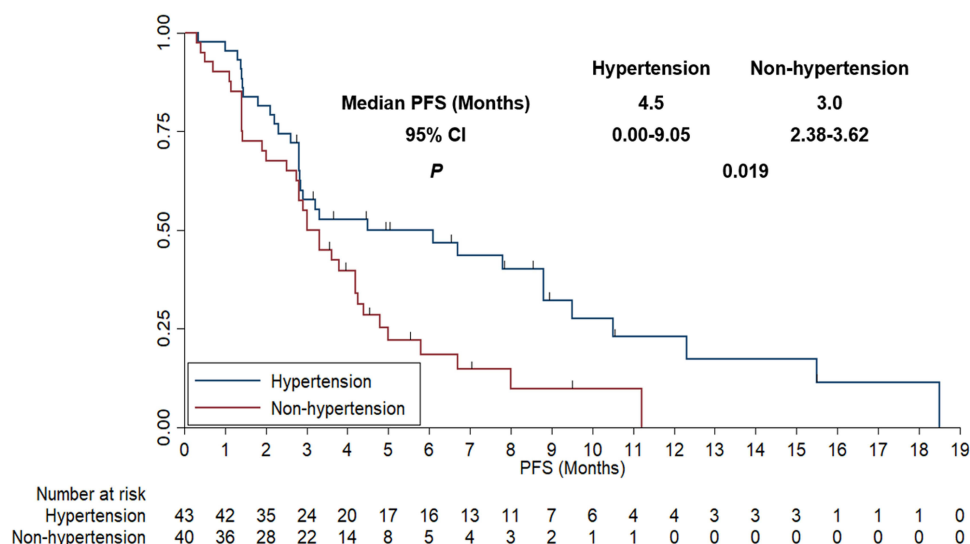


Figure 6 The progression-free survival curve of the 83 patients with advanced or metastatic esophageal squamous cell carcinoma who received anlotinib monotherapy according to hypertension status.

However, it should be noted that patients with ECOG performance status 0–1 score conferred a significantly longer PFS than those with 2 score in univariate analysis (median PFS: 4.5 vs 2.5 months, $P = 0.013$). As a result, our study exhibited that performance status of 0–1 score might be used as a potential biomarker to predict the prognosis of anlotinib monotherapy. However, this conclusion should be interpreted with caution. To the best of our knowledge, patients with ECOG higher score had a trend to correlate with worse prognosis regardless of the therapeutic regimens.²⁶ Therefore, the conclusion that ECOG performance status might be used as a potential biomarker might be confirmed in prospective clinical trials subsequently. Additionally, it was noteworthy that a total of 20 patients (24.1%) had received PD-1 blockades previously, which was strikingly different from the baseline characteristics in the ALTER1102 trial (patients rarely received PD-1 blockades administration). We speculated the discrepancy might be attributed to the different time periods of patient enrollment. The enrollment period was from January 2016 to May 2018 in the ALTER1102 trial, while patients in our study were included from July 2018 to November 2021. A considerable number of patients in our study were accessible for the PD-1 blockades to some extent, which also suggested that PD-1 blockades had become a hot spot for patients with advanced or metastatic ESCC clinically since 2019.²⁷ Interestingly, we also found that patients who received PD-1 blockades administration previously had a trend for superior PFS compared with those who failed to receive PD-1 blockades treatment, although the difference was not statistically significant (median PFS: 4.2 vs 3.0 months, $P = 0.103$). It seemed that the previous PD-1 blockades administration might improve the prognosis of anlotinib monotherapy to some extent. A previous exploratory study indicated that the anti-PD-1 therapy might restore T cells from exhausted status to activity status, resulting in the enhancement of tumor-killing activity.²⁸ Accordingly, we noticed that a recent reported study initiated by Aoki et al. investigated a similar topic clinically.²⁹ A total of 36 patients with hepatocellular carcinoma (HCC) who had failed the prior PD-1/PD-L1 blockades therapy were

Table 4 Multivariate Cox Analysis for PFS Based on Baseline Characteristic and Hypertension Status

Characteristics	HR	95% CI	P
ECOG performance status score 0–1 vs 2	0.56	0.22–0.89	0.021
Hypertension status Hypertension vs non-hypertension	0.67	0.31–0.91	0.029

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, confidence interval.

included and treated with lenvatinib (another antiangiogenic TKI) monotherapy, which yielded an ORR of 55.6%, DCR of 86.1% and median PFS and OS of 10 and 15.8 months, respectively. All of the efficacy outcomes were better than those of lenvatinib treatment alone. This study was closely consistent with our study. The superior PFS of anlotinib monotherapy after PD-1 blockades administration in our study suggested the potentially synergistic action for cancer therapy, which was in accordance with the result that was observed in patients with HCC who received atezolizumab plus bevacizumab combination therapy.³⁰ However, the conclusion that the efficacy of anlotinib monotherapy might be more profound after PD-1 blockades administration should be elucidated in prospective clinical trials subsequently. Additionally, OS was also measured in our study. The median OS in our study was longer than that of anlotinib group in the ALTER1102 trial (median OS: 7.8 vs 6.1 months).¹² Additionally, OS in our study was longer than that of a previously reported study regarding apatinib for ESCC (median OS: 7.8 vs 5.8 months).²⁴ We speculated the possible explanation could be attributed to the fact that continuous PD-1 blockades and antiangiogenic targeted drugs were licensed in China since 2018.³¹ Interestingly, a recent network meta-analysis initiated by Lin et al. investigated the comparative efficacy of the different regimens for previously treated patients with advanced ESCC.³² The conclusion suggested that the administration of PD-1 blockades, especially camrelizumab was likely to be the optimal regimen for patients with ESCC and provided survival benefit for the patients. As a result, considerable PD-1 blockades and targeted drugs were still available for the patients with advanced or metastatic ESCC when they progressed after anlotinib administration in our study, thus providing the patients with survival benefits consecutively.

Furthermore, no grade 5 adverse reactions were observed and no unexpected adverse signal was detected during anlotinib administration. The overall adverse reactions to anlotinib were acceptable and controllable, which was consistent with the safety profile of anlotinib monotherapy in a previous study.³³ Additionally, the relatively common adverse reactions were hypertension, fatigue, weight loss, diarrhea, hand-foot syndrome, ASL/ALT elevation, nausea and vomiting, proteinuria, dysphonia, hematological toxicity, stomatitis and hemorrhage, which was consistent with the profile of the adverse reactions commonly observed in the ALTER1102 trial.¹² Interestingly, it should be noted that the overall incidence was slightly lower than that of the ALTER1102 study numerically. Besides, most of the adverse reactions recorded in this study were those did not require laboratory examination. Also, the incidence of biochemical test adverse reactions including ASL/ALT elevation, hematological toxicity and proteinuria was lower than that in clinical trials, which was in line with a previous real-world study regarding anlotinib monotherapy.³⁴ We speculated the explanation might be attributed to the retrospective design of our study, considerable patients failed to receive relevant biochemical examinations in time, and some adverse actions were missing and recorded incompletely, thus contributing to a potential bias and the relatively low incidence of adverse reactions in our study. Furthermore, hypertension was also the most common adverse reaction in our study with an incidence of 51.8% and grade 3–4 incidence of 15.7%, which was in accordance with the incidence of anlotinib monotherapy in solid tumor.³⁵ To our knowledge, hypertension was a common adverse reaction associated with treatment with antiangiogenic targeted drugs that acted on the VEGF/VEGFR pathway. However, the mechanisms underlying this have not been interpreted thoroughly.³⁶ Several previous studies suggested that the inhibition of VEGFR in vascular endothelial cells decreased the production of nitric oxide and prostacyclins, thus leading to increased blood pressure.³⁷ Given that hypertension was the most common adverse reaction that was easy to monitor, this might attenuate the potential bias in a retrospective study to some extent, as the prognostic association analysis was mainly focused on hypertension in our study. The relevance analysis indicated that patients with hypertension had a longer PFS than those with non-hypertension, and hypertension induced by anlotinib treatment might be used as a potential biomarker to predict PFS of patients with ESCC. This finding in our study was consistent with that of considerable retrospective studies regarding anlotinib monotherapy in other cancers.^{14,15} Furthermore, a recent post-hoc analysis of the ALTER1102 trial initiated by Huang et al. investigated the association between treatment-induced hypertension and efficacy of anlotinib in recurrent or metastatic ESCC.³⁸ The results indicated that a total of 59 patients (54%) were observed to have treatment-induced hypertension and they had a longer PFS and OS and higher ORR, which was consistent with the association analysis between hypertension and PFS in our study. To our knowledge, hypertension induced by angiogenesis inhibitors might result from the inherent host biology that caused the difference in VEGF/VEGFR inhibitors and served as a biomarker for the efficacy of angiogenesis inhibitors.³⁹ Collectively, the conclusion that patients with hypertension might have superior PFS should be validated in large-scale prospective trials

subsequently. Additionally, from the clinical feasibility view for investigators and patients, more active attempts should be used to control hypertension instead of immediate reduction in drug dosage or interruption of the treatment when hypertension was detected during anlotinib administration.⁴⁰

From the objective view, limitations were observed in our study, inevitably. Firstly, the sample size was comparatively small for a real-world study, with only 83 patients enrolled. Feasibility and safety profile of anlotinib monotherapy still need to be elucidated in more patients. Secondly, some objective bias could not be avoided in a retrospective study, for instance, the maturity of PFS and OS data was relatively low and the record of adverse reactions in our study was poor compared with a phase III clinical trial. Still, overall, our study provided real-world evidence regarding the efficacy and safety of anlotinib monotherapy among patients with previously treated advanced or metastatic ESCC, and hypertension might be a potential biomarker to predict PFS for patients with ESCC, which could have clinical implications for clinicians.

Acknowledgments

This work was supported by grants from Joint project of Henan Provincial Health Commission (No. LHGJ20190045).

Disclosure

The authors declare that there are no conflicts of interest.

References

1. Sardaro A, Ferrari C, Carbonara R, et al. Synergism between immunotherapy and radiotherapy in esophageal cancer: an overview of current knowledge and future perspectives. *Cancer Biother Radiopharm*. 2021;36(2):123–132. doi:10.1089/cbr.2020.3643
2. He F, Wang J, Liu L, et al. Esophageal cancer: trends in incidence and mortality in China from 2005 to 2015. *Cancer Med*. 2021;10(5):1839–1847. doi:10.1002/cam4.3647
3. Yang CS, Chen XL. Research on esophageal cancer: with personal perspectives from studies in China and Kenya. *Int J Cancer*. 2021;149(2):264–276. doi:10.1002/ijc.33421
4. He S, Xu J, Liu X, Zhen Y. Advances and challenges in the treatment of esophageal cancer. *Acta Pharm Sin B*. 2021;11(11):3379–3392. doi:10.1016/j.apsb.2021.03.008
5. Mahmoudian RA, Mozhgani S, Abbaszadegan MR, et al. Correlation between the immune checkpoints and EMT genes proposes potential prognostic and therapeutic targets in ESCC. *J Mol Histol*. 2021;52(3):597–609. doi:10.1007/s10735-021-09971-3
6. Hayashi K, Ando N, Watanabe H, et al. Phase II evaluation of protracted infusion of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG) trial (JCOG9407). *Jpn J Clin Oncol*. 2001;31(9):419–423. doi:10.1093/jjco/hye090
7. Liu Y, Ren Z, Yuan L, et al. Paclitaxel plus cisplatin vs. 5-fluorouracil plus cisplatin as first-line treatment for patients with advanced squamous cell esophageal cancer. *Am J Cancer Res*. 2016;6(10):2345–2350.
8. Kojima T, Shah MA, Muro K, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol*. 2020;38(35):4138–4148. doi:10.1200/jco.20.01888
9. Lu Y, Guan L, Xu M, Wang F. The efficacy and safety of antibodies targeting PD-1 for treatment in advanced esophageal cancer: a systematic review and meta-analysis. *Transl Oncol*. 2021;14(6):101083. doi:10.1016/j.tranon.2021.101083
10. Jin Z, Shen J, Wang C, et al. Narrative review of pembrolizumab for the treatment of esophageal cancer: evidence and outlook. *Ann Transl Med*. 2021;9(14):1189. doi:10.21037/atm-21-2804
11. Han B, Li K, Wang Q, et al. Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: the ALTER 0303 phase 3 randomized clinical trial. *JAMA Oncol*. 2018;4(11):1569–1575. doi:10.1001/jamaoncol.2018.3039
12. Huang J, Xiao J, Fang W, et al. Anlotinib for previously treated advanced or metastatic esophageal squamous cell carcinoma: a double-blind randomized phase 2 trial. *Cancer Med*. 2021;10(5):1681–1689. doi:10.1002/cam4.3771
13. Su R, Zhu J, Wu S, Luo H, He Y. Prognostic Significance of Platelet (PLT) and Platelet to Mean Platelet Volume (PLT/MPV) ratio during apatinib second-line or late-line treatment in advanced esophageal squamous cell carcinoma patients. *Technol Cancer Res Treat*. 2022;21:15330338211072974. doi:10.1177/15330338211072974
14. Song PF, Xu N, Efficacy LQ. Safety of anlotinib for elderly patients with previously treated extensive-stage SCLC and the prognostic significance of common adverse reactions. *Cancer Manag Res*. 2020;12:11133–11143. doi:10.2147/cmar.s275624
15. Cheng JD, Chai LX, Zhao ZP, Hao YY, Efficacy LS. Safety of anlotinib for patients with advanced NSCLC who progressed after standard regimens and the preliminary analysis of an efficacy predictor. *Cancer Manag Res*. 2020;12:5641–5650. doi:10.2147/cmar.s253366
16. Zhang B, Qi L, Wang X, et al. Phase II clinical trial using camrelizumab combined with apatinib and chemotherapy as the first-line treatment of advanced esophageal squamous cell carcinoma. *Cancer Commun*. 2020;40(12):711–720. doi:10.1002/cac2.12119
17. Yang YM, Hong P, Xu WW, He QY, Li B. Advances in targeted therapy for esophageal cancer. *Signal Transduct Target Ther*. 2020;5(1):229. doi:10.1038/s41392-020-00323-3
18. Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(11):1506–1517. doi:10.1016/s1470-2045(19)30626-6

19. Peng C, Cohen DJ. Advances in the pharmacotherapeutic management of esophageal squamous cell carcinoma. *Expert Opin Pharmacother*. 2021;22(1):93–107. doi:10.1080/14656566.2020.1813278
20. Sun JM, Shen L, Shah MA, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2021;398(10302):759–771. doi:10.1016/s0140-6736(21)01234-4
21. Luo H, Lu J, Bai Y, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. *JAMA*. 2021;326(10):916–925. doi:10.1001/jama.2021.12836
22. Doki Y, Ajani JA, Kato K, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N Engl J Med*. 2022;386(5):449–462. doi:10.1056/NEJMoa2111380
23. Wu D, Nie J, Dai L, et al. Salvage treatment with anlotinib for advanced non-small cell lung cancer. *Thorac Cancer*. 2019;10(7):1590–1596. doi:10.1111/1759-7714.13120
24. Chu L, Chen Y, Liu Q, et al. A phase II study of apatinib in patients with chemotherapy-refractory esophageal squamous cell carcinoma (ESO-Shanghai 11). *Oncologist*. 2021;26(6):e925–e935. doi:10.1002/onco.13668
25. Zhang K, Ma X, Gao H, et al. Efficacy and safety of anlotinib in advanced non-small cell lung cancer: a real-world study. *Cancer Manag Res*. 2020;12:3409–3417. doi:10.2147/cmar.s246000
26. Bai M, Li ZG, Ba Y. Influence of KDR genetic variation on the efficacy and safety of patients with chemotherapy refractory metastatic CRC who received apatinib treatment. *Int J Gen Med*. 2021;14:1041–1055. doi:10.2147/ijgm.s300968
27. Smyth EC, Gambardella V, Cervantes A, Fleitas T. Checkpoint inhibitors for gastroesophageal cancers: dissecting heterogeneity to better understand their role in first-line and adjuvant therapy. *Ann Oncol*. 2021;32(5):590–599. doi:10.1016/j.annonc.2021.02.004
28. Yi M, Qin S, Zhao W, et al. The role of neoantigen in immune checkpoint blockade therapy. *Exp Hematol Oncol*. 2018;7:1. doi:10.1186/s40164-018-0120-y
29. Aoki T, Kudo M, Ueshima K, et al. Exploratory analysis of lenvatinib therapy in patients with unresectable hepatocellular carcinoma who have failed prior PD-1/PD-L1 checkpoint blockade. *Cancers*. 2020;12:10. doi:10.3390/cancers12103048
30. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
31. Jiang M, Zhao L, Cui X, et al. Cooperating minimalist nanovaccine with PD-1 blockade for effective and feasible cancer immunotherapy. *J Adv Res*. 2022;35:49–60. doi:10.1016/j.jare.2021.08.011
32. Lin S, Liu T, Chen J, Li G, Dang J. Comparative efficacy of treatments for previously treated patients with advanced esophageal and esophagogastric junction cancer: a network meta-analysis. *PLoS One*. 2021;16(6):e0252751. doi:10.1371/journal.pone.0252751
33. Jiang HT, Li W, Zhang B, Gong Q, Qie HL. Efficacy and safety of anlotinib monotherapy as third-line therapy for elderly patients with non-small cell lung cancer: a real-world exploratory study. *Int J Gen Med*. 2021;14:7625–7637. doi:10.2147/ijgm.s334436
34. Gao X, Peng L, Zhang L, et al. Real-world efficacy and safety of anlotinib as third- or further-line treatment in refractory small cell lung cancer. *J Cancer Res Clin Oncol*. 2021. doi:10.1007/s00432-021-03848-4
35. Li S. Anlotinib: a novel targeted drug for bone and soft tissue sarcoma. *Front Oncol*. 2021;11:664853. doi:10.3389/fonc.2021.664853
36. Li M, Kroetz DL. Bevacizumab-induced hypertension: clinical presentation and molecular understanding. *Pharmacol Ther*. 2018;182:152–160. doi:10.1016/j.pharmthera.2017.08.012
37. Tang JR, Markham NE, Lin YJ, et al. Inhaled nitric oxide attenuates pulmonary hypertension and improves lung growth in infant rats after neonatal treatment with a VEGF receptor inhibitor. *Am J Physiol Lung Cell Mol Physiol*. 2004;287(2):L344–351. doi:10.1152/ajplung.00291.2003
38. Song Y, Xiao J, Fang W, et al. The relationship between treatment-induced hypertension and efficacy of anlotinib in recurrent or metastatic esophageal squamous cell carcinoma. *Cancer Biol Med*. 2021;18(2):562–568. doi:10.20892/j.issn.2095-3941.2020.0187
39. Sanidas E, Papadopoulos DP, Velliou M, et al. The role of angiogenesis inhibitors in hypertension: following “ariadne’s thread”. *Am J Hypertens*. 2018;31(9):961–969. doi:10.1093/ajh/hpy087
40. Aparicio-Gallego G, Afonso-Afonso FJ, León-Mateos L, et al. Molecular basis of hypertension side effects induced by sunitinib. *Anticancer Drugs*. 2011;22(1):1–8. doi:10.1097/CAD.0b013e3283403806

Cancer Management and Research

Dovepress

Publish your work in this journal

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>