

Clinical analysis of ECOG PS and adverse reactions in patients with anlotinib at advanced NSCLC as the third or further line treatment: a retrospective observational study

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Abstract

Background: Previous studies have shown that anlotinib be a decent choice in third- or further line treatment of advanced NSCLC. However, the study analysis of relationship between Eastern Cooperative Oncology Group performance status(ECOG PS) and adverse reactions in advanced NSCLC with anlotinib therapy is less.

Methods: We evaluated the efficacy and toxicity of anlotinib in patients with previously treated advanced NSCLC from June 2018 to March 2019. Survival analysis was performed by the Kaplan–Meier method.

Results: According to ECOG PS divided into PS 0-1 group(n=63) and PS 2 group(n=28) . The PS 0-1 of median progression-free survival (mPFS, 5.5 vs.2.7 months, $P=0.05$) , overall survival (mOS, 9.2 vs.4.7 months $P=0.05$) was longer than PS 2. The PS 0-1 of objective remission rate(ORR, 45.1% vs 6.6%), disease control rate(DCR, 8.8% vs 1.1%) was significantly more than PS 2. The PS 0-1 group of II adverse reactions was high than PS 2 group(52.3% vs 32.1%), but the III-IV adverse reactions were less than PS 2 group(9.5% vs 10.7%). Moreover, multivariate analysis indicated that PS was independent risk factor of PFS(HR=2.816, 95%CI 1.661-4.773 $P<0.0001$) as well as OS(HR=3.188, 95%CI 1.789-5.682 $P=0.0001$) for anlotinib therapy in NSCLC.

Conclusions: Patients in advanced NSCLC with PS 0–1 get better PFS and OS than PS 2 followed by anlotinib treatment in NSCLC. Advanced lung squamous cell carcinoma(LUSC) received anlotinib treatment with the same efficacy comparable to adenocarcinoma, and patients with PS 0-1 may benefit the most than PS 2.

Background

According to the latest global cancer data in 2018, lung cancer is still the main cause of morbidity and mortality in the worldwide^[1]. NSCLC accounted for more than 85% of all lung cancer. Nearly 70% of NSCLC patients were diagnosed lately^[2–3], and lost the chance of radical surgery. Previous studies have shown that Doxorubicin and pemetrexed are standard second-line therapies for advanced non-sensitive mutations of NSCLC. However, the median PFS(mPFS) was only 2.9 months, and the median overall survival(mOS) was only 7–8 months, and the low efficacy and adverse reactions of chemotherapy drugs were often intolerable^[4–6]. For patients with non-sensitive mutations of advanced NSCLC who developed progressive disease after first and second-line treatment, and before anlotinib was found, there is no standard three-line treatment, so it is urgent to find new treatment methods.

Tyrosine kinase is a key component of intracellular signal transduction pathway, and many cancer cells show abnormal tyrosine kinase activity^[7–8]. To control this abnormal activity, the researchers found that small molecule inhibitors could block tyrosine kinase-mediated phosphorylation^[9]. Molecular targeting therapy with tyrosine kinase inhibitors is usually more specific and less toxic to cancer cells than cytotoxic chemotherapy drugs^[10]. As a new type of small molecule multi-target TKI, anlotinib has broad-spectrum anti-angiogenesis and anti-tumor growth effects, especially in the inhibition of targets such as vascular endothelial growth factor R2(VEGFR2), vascular endothelial growth factor R3(VEGFR3), PDGFR β and c-Kit^[11–12]. Many studies have further identified that anlotinib has broader and more effective anti-tumor effects in vivo than Sunitinib and Sorafenib^[11–12, 13]. Moreover, pre-Phase II and Phase III clinical studies had preliminarily validated the efficacy and safety of anlotinib in the treatment of advanced NSCLC^[14–15].

Many studies shown that performance status (PS) is the strongest predictor of survival in patients with advanced NSCLC^[16–17]. It has a greater impact on the choice of treatment options and drug tolerance, and is also an important indicator reflecting the severity of patients' condition for advanced NSCLC treatment^[18]. And Felip *et al.*^[19] showed that the advanced lung squamous cell cancer(LUSC) of patients in ECOG PS 2 received the nivolumab with a worse OS and difficult to treat, and poor prognosis. Furthermore, the antiangiogenic drugs of bevacizumab with PS 0-1 were more effective or less adverse drug reactions than PS 2 in non-squamous of NSCLC^[20]. So what the antiangiogenic drugs of anlotinib relationship with ECOG PS both in adenocarcinoma and squamous cell carcinoma, there were less studies reported that. Moreover, there are still some patients with poor efficacy and intolerance of adverse reactions of anlotinib, and which groups of people can get the best effect from anlotinib

treatment, which is rarely reported. In this study, we retrospectively analyzed the results of anlotinib treatment with PS 0–2 patients in our cohort.

Methods

2.1 Main grouping criteria

The inclusion criteria were as follows: (1) recurrent or advanced NSCLC (stage IIIB, IIIC, or IV, American Joint Committee on Cancer Cancer Staging Manual, 8th edition) with failure of at least two lines of chemotherapy or EGFR-TKIs targeted drugs, and the third-line treatment with single-drug anlotinib. (2) The patients were older than 18 years old, Karnofsky Performance Status was greater than 60 or PS was 0–2. (3) All patients were diagnosed as advanced NSCLC by histopathology or cytology combined with imaging examination. (4) All patients should receive two courses of treatment and then progress, with complete imaging data and at least one assessable target lesion. The size of the lesion could be measured by CT. (5) The patient of relevant laboratory tests and cardiopulmonary function were basically normal. **The exclusion criteria were as follows:** (1) Patients with poor physical condition can not tolerate adverse drug reactions. (2) Patients with brain metastasis. (3) Patients with poor compliance or abandonment of treatment. (4) Patients have major organ failure, such as severe liver disease, nephropathy, respiratory diseases or uncontrollable hypertension, diabetes and other chronic diseases. (5) Patients with other malignant tumors and incomplete clinical data. (6) Patients with small cell lung cancer, including lung cancer mixed with non-small cell lung cancer.

2.2 Therapeutic method

This study was approved by the ethics institution committee of First Affiliated Hospital of Nanchang University, Jiangxi P.R. China. All patients received the treatment of anlotinib must be obtained the consent and signed the informed consent form. Anlotinib hydrochloride capsules (Fukewei, 12 mg, 10 mg, 8 mg, Zhengda Tianqing Pharmaceutical company Co., Ltd), once a day, two weeks and then stop for a week, three weeks for a course of treatment. Adjust dosage according to adverse reactions, and continue current dosage treatment if no obvious adverse reactions occur. If grade 2, 3 and 4 adverse reactions are intolerable, the doctor should base on patient's tolerance and decided to whether or not to take a drug reduction or discontinued, and the reduction is 10 mg or 8 mg, until the disease progresses. In the course of treatment, according to the results of relevant examinations and adverse reactions of patients, the best treatment measures can be taken to ensure the implementation of the treatment plan.

2.3 Post-treatment evaluation criteria

Chest and abdominal Computer Tomography (CT), bone scan and craniocerebral nuclear magnetic resonance (MRI) were reexamined after two cycles or when clinical symptoms worsened of anlotinib treatment. The therapeutic effect was evaluated according to the Response Evaluation Criteria in Solid Tumors 1.1(RECIST1.1) established by the International Union against Cancer (UICC). It can be divided into complete response (CR), partial response(PR), stable disease(SD) and progressive disease(PD). The clinical benefit is that the curative effect is maintained for more than 4 weeks. Objective remission rate (ORR)= (CR + PR)/ total cases * 100%, Disease control rate(DCR) = (CR + PR + SD) / total cases * 100%. PFS was calculated from the start time of taking anlotinib to the date of disease progression or death from any cause. OS was calculated from the start time of taken anlotinib to the date of death or latest follow-up time. Adverse reactions were evaluated according to the Common Toxicity Criteria (CTC) 3.0 issued by the National Cancer Institute(NCI) in 2006.

2.4 Statistical methods

Patients were classified into two groups according to their PS and were compared using the chi-squared test or Fisher's exact test for qualitative variables. The Kaplan-Meier method was used to calculate survival rates, univariate and multivariate prognostic analysis was used to Cox regression model and calculate the hazard ratio (HR) and 95% confidence interval (CI), to find the independent prognostic factor. Statistical analysis was performed by using SPSS 22.0 software package(SPSS Inc., Chicago, IL, USA), statistical results $P < 0.05$ was considered significantly. Review Manager 5.3 was applied to forest figure with univariate significant factors.

Results

3.1 Baseline patient characteristics

We retrospectively collected the medical data of advanced NSCLC patients between June 2018 and April 2019, the follow-up time of cut-off date was 30 June 2020, and by the end of follow-up time with a median of 15 months. There were 134 patients with NSCLC who were treated with anlotinib, while a total of 91 NSCLC patients were enrolled. Intolerance of adverse reactions and was not oral anlotinib in fifteen patients, seven patients PS was 3, twenty-one previous have brain metastases, so those patients were exclusion. At the end of the follow-up, the patients were still in oral anlotinib and the disease was not progress, and the patients could not be contacted during oral anlotinib, those of patients as a censored case.(Fig. 1). According to pathological type, there were 43 patients in adenocarcinoma and 48 in squamous. The previous EGFR mutations(n = 22), ALK mutations(n = 2) and KRAS mutations(n = 2) were detected. Twenty patients received the EGFR-TKIs treatment(Gefitinib, Erlotinib, Eritinib), and sixty-five received the platinum containing chemotherapy, two patients recived ALK inhibitors(Crizotinib), and four patients recived the gemcitabine or pemetrexed monotherapy. The characteristics of the study population are shown in Table 1.

Table 1
Patients' characteristics and comparison between PS 0–1 and PS 2 group with anlotinib therapy

Characteristic		N	PS 0–1 group	PS 2 group	χ^2	P
Gender	Male	73	51	22	4.62	0.035
	Female	18	17	1		
Age(years)	≤ 60	33	24	9	0.109	0.741
	≥60	58	44	14		
Treatment of base line	3 line	40	31	9	0.291	0.59
	≥3 line	51	37	14		
Smoking index^a	No	41	35	6	4.473	0.034
	Yes	50	33	17		
Pathological type	Adenocarcinoma	43	34	9	0.815	0.367
	Squamous	48	34	14		
EGFR mutation	No	22	17	5	0.124	0.94
	Yes	22	16	6		
	Unknown	47	35	12		
TNM stage	IIIB-C	10	7	3	0.133	0.709
	IV	81	61	20		
Liver metastase	No	71	54	17	0.303	0.582
	Yes	20	14	6		
Metastase site	< 3 organs	59	48	11	3.906	0.048
	≥ 3 organs	32	20	12		
Platinum containing chemotherapy	Yes	65	47	18	0.704	0.401
	No	26	21	5		
Malignant pleural effusion	No	69	53	16	0.658	0.417
	Yes	22	15	2		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; a, smoking index = number of cigarettes per day × smoking age, and smoking index 400 as the Yes or No groups.

RECIST	ECOG PS 0–1		ECOG PS 2	
	N	Percentage	N	Percentage
CR	1	1.1%	0	0%
PR	7	7.7%	1	1.1%
SD	33	36.3%	5	5.5%
PD	27	29.7%	17	18.7%
ORR	8	8.8%	1	1.1%
DCR	41	45.1%	6	6.6%

Abbreviations: CR, Complete Response; PR, Partial Response; SD, Stable Disease; PD, Progressive Disease; ORR, Objective remission rate; DCR, Disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status.

3.2 Analysis of Short-term Therapeutic Effect and Therapeutic Effect

There were 91 patients could be evaluated, there were forty-nine patients deaths from any cause. The short-term therapeutic of 91 patients were follows: CR (n = 1), PR(n = 8), SD (n = 38)and PD(n = 44). According to ECOG PS divided into two groups, the PS 0–1 of ORR(45.1% vs 6.6%), DCR(8.8% vs 1.1%) was significantly more than PS 2. (Table 2) .

3.3 Univariate and Multivariate Survival Analyses in All Patients

The median PFS was 4.7 months, the mediate OS was 6.4 months for received anlotinib. Univariate and multivariate analyses were performed to evaluate the predictive impact of anlotinib and other clinicopathological factors on OS and PFS. The results of univariate analyses showed that ECOG PS 2 ($P= 0.000$, Fig. 2A), liver metastasis ($P= 0.032$), metastasis sites more than 3 ($P = 0.019$) were the poor prognostic factors for PFS. ECOG PS ($P= 0.000$, Fig. 2B); smoking ($P= 0.02$), treatment of base line ($P= 0.013$), liver metastasis ($P= 0.017$) and metastasis site ($P= 0.011$) were significantly associated with OS. Neither pathological type nor previous EGFR mutation was found to be associated with PFS or OS.(Table 3)

Table 3
Univariate analysis of PFS and OS among 91 patients with different clinical features

Characteristic		N	mPFS			mOS		
			months	HR(95%CI)	P	months	HR(95%CI)	P
Gender	Male	73	5.1	Reference	0.524	6.4	Reference	0.496
	Female	18	3.8	1.209(0.674–2.172)		6.7	1.272(0.636–2.544)	
Age(years)	≤ 60	33	5.2	Reference	0.547	6.4	Reference	0.361
	≥60	58	4.6	1.163(0.711–1.902)		6.6	1.32(0.728–2.395)	
Treatment of base line	3 line	40	6.1	Reference	0.079	9.5	Reference	0.016
	≥3 line	51	4	1.525(0.952–2.442)		5.1	2.033(1.142–3.618)	
Smoking index	No	41	5.6	Reference	0.046	9.5	Reference	0.023
	Yes	50	4.6	1.632(1.05–2.536)		5.6	1.977(1.099–3.558)	
Pathological type	Adenocarcinoma	43	3.8	Reference	0.457	6.1	Reference	0.289
	Squamous	48	5.2	0.839(0.528–1.333)		7.4	0.743(0.429–1.287)	
EGFR mutation	No	22	3.3	Reference	0.602	5.1	Reference	0.203
	Yes	22	4.1	1.152(0.597–2.221)	0.673	6.1	1.027(0.488–2.161)	0.943
	Unknown	47	5.2	0.868(0.487–1.547)	0.63	7	0.613(0.31–1.212)	0.159
TNM stage	IIIB-C	10	5.2	Reference	0.565	6.4	Reference	0.465
	IV	81	4.6	1.242(0.594–2.593)		6.6	1.412(0.56–3.559)	
Liver metastase	No	71	5.2	Reference	0.037	8.4	Reference	0.02
	Yes	20	3.3	1.805(1.038–3.141)		4.4	2.055(1.119–3.773)	
Metastase sites	< 3 organs	59	5.4	Reference	0.021	9.2	Reference	0.013
	≥ 3 organs	32	3.2	1.759(1.087–2.846)		4.6	2.029(1.161–3.545)	
Platinum containing chemotherapy	Yes	65	4.7	Reference	0.75	6.4	Reference	0.696
	No	26	5.2	0.918(0.543–1.552)		6.6	1.128(0.617–2.062)	
Malignant pleural effusion	No	69	5.1	Reference	0.848	7.4	Reference	0.168
	Yes	22	3.8	1.055(0.612–1.818)		4.6	1.53(0.836–2.798)	
ECOG PS	0–1	68	5.5	Reference	0.0001	9.2	Reference	0.0001
	2	23	2.7	2.944(1.745–4.965)		4.3	3.199(1.806–5.666)	

Characteristic		N	mPFS			mOS		
			months	HR(95%CI)	P	months	HR(95%CI)	P
Adenocarcinoma + ECOG PS	0-1	34	4.1	Reference	0.008	6.6	Reference	0.068
	2	9	2.2	3.042(1.337-6.922)		4.4	2.188(0.945-5.066)	
Squamous + ECOG PS	0-1	34	6.7	Reference	0.001	8.1	Reference	0.0001
	2	14	2.95	3.14(1.567-6.293)		3.2	4.686(2.09-10.508)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

In the multivariate analysis, Cox proportional hazards regression models showed that ECOG PS(HR = 2.816, 95%CI: 1.661–4.773, $P < 0.0001$) and Metastase sites(HR = 1.632, 95%CI 1.004–2.656, $P < 0.05$) was independent risk factors of PFS. Moreover, ECOG PS 2(HR = 3.188, 95%CI 1.789–5.682, $P < 0.0001$) and treatment of base line(HR = 2.013, 95%CI 1.125–3.604, $P < 0.05$) was independent risk factors of OS. (Table 4).

Table 4
Multivariate analysis of Anlotinib therapy in advance NSCLC

Variable	PFS			OS		
	P	HR	95%CI	P	HR	95%CI
ECOG PS(0-1/2)	0.0001	2.816	1.661-4.773	0.0001	3.188	1.789-5.682
Liver metastase(No/Yes)	0.275	1.388	0.771-2.5	0.595	1.206	0.605-2.403
Metastase sites(≤ 3 organs/ ≥ 3 organs)	0.048	1.632	1.004-2.656	0.132	1.614	0.866-3.007
Smoking index (No/Yes)	0.176	1.422	0.854-2.367	0.071	1.747	0.953-3.201
Treatment of base line(3line/ ≥ 3 line)				0.018	2.013	1.125-3.604

Table 5 Adverse reactions of 91 patients with advanced NSCLC treated with alotinib					
Adverse event	No.patients (%)	PS 0–1(n, %)		PS 2(n, %)	
		I-II grade	III-IV grade	I-II grade	III-IV grade
Hand-foot syndrome	16(17)	9(10)	4(4)	2(2)	1(2)
Hypothyroidism	2(2)	2(2)	0(0)	0(0)	0(0)
Fatigue	13(14)	10(11)	1(1)	1(1)	1(1)
Weight loss	5(5)	3(3)	0(0)	2(2)	0(0)
Anorexia	3(3)	2(2)	0(0)	1(1)	0(0)
Rash	1(1)	0(0)	1(1)	0(0)	0(0)
Intestinal obstruction	1(1)	1(1)	0(0)	0(0)	0(0)
Hypertension	1(1)	1(1)	0(0)	0(0)	0(0)
Hemoptysis	6(6)	3(3)	0(0)	2(2)	1(1)
Serum PLT decline	2(2)	1(1)	0(0)	0(0)	1(1)
Serum ALT rise	1(1)	1(1)	0(0)	0(0)	0(0)

Abbreviations: ALT, alanine aminotransferase; PLT, Platelet

3.4 Subgroups analysis of PFS and OS in ECOG PS

Subgroup analyses were performed pathological type and ECOG PS for anlotinib treatment (Table 3). In squamous + ECOG PS of Subgroup, PS 0–1 group has significantly longer PFS (6.7 vs 2.95 months, $P < 0.05$, Fig. 2C) as well as OS (8.1 vs 3.2 months, $P < 0.0001$, Fig. 2D) than PS 2 group. Moreover, in adenocarcinoma + ECOG PS of subgroup, the result of PS 0–1 had significantly longer PFS than PS 2 (4.1 vs 2.2 months, $P < 0.05$, Fig. 1E); although the OS was no significantly difference between two groups (6.6 vs 4.4 months, $P = 0.0599$, Fig. 2F), the PS 0–1 of OS was nearly two months longer than PS 2.

3.5 Adverse reactions

There were 51 patients with adverse reactions, 5 patients with reduction of 10 mg and 2 patients with reduction of 8 mg. The common adverse reactions were hand-foot syndrome (17%), fatigue (14%), weight loss (5%) and hemoptysis (6%). Other less adverse reactions included hypothyroidism (2%), rash (1%), anorexia (3%), serum PLT decline (3%), hypertension (1%), cerebral infarction (1%) and elevated ALT (1%). The rate of grade 1 adverse reactions was 38.5%, grade 2 adverse reactions was 6.5%, grade 3 adverse reactions was 8.8%, and grade 4 adverse reactions was 1%. Moreover, our study were divided ECOG PS into two groups, the PS 0–1 group of I-II adverse reactions was high than PS 2 group (52.3% vs 32.1%), and III-IV adverse reactions were less than PS 2 group (9.5% vs 10.7%). (Table 5).

Discussion

Most advanced NSCLC patients inevitably have disease progression after first-line and second-line treatment, and need further treatment. A Phase III clinical study (ALTER-0303)^[15] showed that The median OS (9.63 vs 6.3 months, $P = 0.0018$), PFS (5.37 vs 1.4 months, $P < 0.0001$), DCR (81.0% vs 37.1%, $P < 0.0001$) and ORR (9% vs 1%, $P < 0.0001$) of anlotinib were significantly better than those of placebo group, and the adverse reactions were generally tolerable, similar to those reported in previous studies.

In the present study, the result of patients who received anlotinib showed that the median PFS was 4.7 months, and the median OS was 6.4 month. In addition, the ORR and DCR were 9.9% and 51.6%. Although the survival time was shorter than that of ALTER-0303, one of the result was considered that there were 28 patients with PS 2 in this study, this may be an important reason for the difference in survival time. According to Di Maio *et al*^[18] showed that physical condition has a greater impact on the choice of treatment options and drug tolerance, and is also an important indicator reflecting the severity of patients'

condition for advance NSCLC treatment. Furthermore, if we exclude patients with PS 2, the median PFS, OS were 5.5 and 9.2 months, which was similar to the ALTER-0303. And also the same study showed that bevacizumab combined with chemotherapy was an effective and tolerable treatment for NSCLC patients with low PS score^[20]. For patients with PS 2, the median PFS, OS were only 2.7 and 4.3 months. Furthermore, according to analysis of short-term therapeutic effect of anlotinib with PS, the PS 0–1 of ORR(ORR, 45.1% vs 6.6%), DCR(8.8% vs 1.1%) was significantly more than PS 2. On the other hand, the adverse reactions of anlotinib on PS, our result also shows that the PS 0–1 group of I-II adverse reactions was high than PS 2 group(52.3% vs 32.1%), but the III-IV adverse reactions were less than PS 2 group(9.5% vs 10.7%). which may indicated that PS was an important factor affecting the treatment of advanced NSCLC by anlotinib, and high PS may lead to patients' difficulty in benefited from anlotinib treatment.

Previous studies have showed that the growth characteristics of lung squamous cell carcinoma(LUSC) are mainly central type, slow growth, local invasion and low regional lymph node metastasis rate^[2,21-23]. The tumor tissues have relatively rich blood supply, and the main cause of death is that the tumor lesions in the chest are not effectively controlled or local recurrence occurs after treatment^[2,24]. The anti-angiogenic drug bevacizumab combined with paclitaxel and carboplatin has only been approved first-line treatment for advanced non-squamous NSCLC without EGFR mutations^[25-26]. And a multi-center phase II clinical trial of apatinib in third- and further-line for advanced NSCLC showed that apatinib can significantly improved the survival time of advanced non-squamous NSCLC, with PFS 4.7 months, DCR 12.2%, and ORR 68.9%^[2,27].

The characteristics of LUSC is characterized by central type and more cavities, which maybe the result that antiangiogenic drugs bevacizumab and apatinib are prohibited for the treatment of advanced LUSC due to the high risk of bleeding. So what is the efficacy and safety of anlotinib third- and further-line in the treatment of advanced LUSC. We divided the pathological type into adenocarcinoma group(n = 43) and squamous group(n = 48) with unselected PS patients, the result shows that there were not significantly differences between in two groups with OS(7.4 vs 6.1 months, $P > 0.05$) and PFS(5.2 vs 3.8 months, $P > 0.05$). Furthermore, in subgroups analysis the pathological type and ECOG PS for anlotinib treatment, the combination of squamous and PS 0–1 has significantly longer PFS(6.7 vs 2.95 months, $P = 0.001$) as well as OS(8.1 vs 3.2 months, $P < 0.0001$) than PS 2. Moreover, in Adenocarcinoma + ECOG PS of Subgroup, the result of PS 0–1 had significantly longer PFS than PS 2(4.1 vs 2.2 months, $P = 0.0049$); although the OS was no significantly difference between two groups(6.6 vs 4.4 months, $P = 0.068$), the PS 0–1 of OS was nearly two months longer than PS 2. This study may shows that the advanced LUSC recived anlotinib treatment with the same efficacy which is comparable to adenocarcinoma, advanced LUSC patients with PS 0–1 and recived anlotinib treatment may benefit the most than PS 2, no matter in mPFS or mOS.

The number of metastasis organs in advanced lung cancer is an important factor for survival and prognosis of patients, the more metastasis organs, the worse prognosis^[28-29]. Patients with liver metastases are associated with poor outcomes and the worst prognosis (median PFS 1.15 vs 3.24months, median OS 3–4 vs 5-8months) than non-liver metastases in the advanced NSCLC^[30-32]. Therefore, a study of bevacizumab in the treatment of advanced non-squamous of NSCLC patients with liver metastasis shows that bevacizumab regimens subgroup was associated with significantly longer PFS(4.2 vs 2.6 months, $P < 0.01$) and OS(7.1 vs 4.4 months, $P < 0.01$) than non-bevacizumab regimens subgroups in patients with baseline liver metastases^[33]. So what is the effect of anlotinib in the treatment of advanced NSCLC with liver metastasis?. In our study, the patients was divided into two groups according to the number of metastatic sites in advanced NSCLC. The ≥ 3 metastatic sites of mPFS(3.2 vs 5.4months, $P = 0.021$) and mOS(4.6 vs 9.2months, $P = 0.013$) in patients with anlotinib was significantly shorter than < 3 metastatic sites, and also was an independent risk factor for PFS(HR = 1.632, 95%CI: 1.004–2.656, $P < 0.05$). Furthermore, we made a subgroup univariate analysis of liver metastasis, the patients oraled the anlotinib showed that non-liver metastases of median OS(8.4 vs 4.4months, $P < 0.05$) and PFS(5.4 vs 3.2 months, $P < 0.05$) was longer than liver metastases, the liver metastases patients with higher costs and health care resource. Our study may be considered most similar to that of research^[31-34], which examined the prognostic effect of liver metastases had a significantly shorter OS.

The clinical studies of anlotinib in the treatment of advanced NSCLC have shown better efficacy and survival benefits. However, the current study has several limitations. Firstly, because the study was a retrospective analysis, the small sample size, the results are easy to be affected by many other factors, and also lack of information regarding quality-of-life benefits. Secondly,

most patients take anlotinib outside the hospital, many syndromes were not found in the course of treatment, and the related syndromes were not given timely intervention, which made the later related syndromes more serious. Although the data of patients for analysis was retrospective, the patients received anlotinib treatment were benefited and adverse reactions can be tolerated.

In conclusion, the present study showed that the single drug of anlotinib has definite efficacy and mild adverse reactions in the treatment of advanced NSCLC. Furthermore, the patients in advanced NSCLC with an ECOG PS 0–1 get better PFS and OS than PS2 followed by anlotinib treatment. And the results of univariate and multivariate analyses show that the patients with PS score of 0–1, no liver metastasis, squamous cell carcinoma, third-line treatment and non-smoking may get better curative effect. In adverse reactions, the PS 0–1 of patients were more tolerant than PS 2. All of that may show us that the importance of PS scores for advanced NSCLC received anlotinib treatment.

Declarations

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Disclosure of Potential Conflicts of Interest

The authors declare that they have no competing interests.

Ethical approval

This study was a retrospective observational study and all patients received the treatment of anlotinib must be obtained the consent and signed the informed consent form. Moreover, the present study has been reviewed and approved by the First Affiliated Hospital of Nanchang University, Nanchang, China.

Authors' contributions

WG Gu and MB Hu were involved in Case collected the data and patients follow-up. WG Gu, JX Deng were responsible for the conception and design of the study, assisted with the statistical analysis and wrote the manuscript. F Qiu and Y Feng contributed to help data analysis and corrected the manuscript. All authors approved the manuscript prior to submission.

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Date availability statement

The data generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Figures

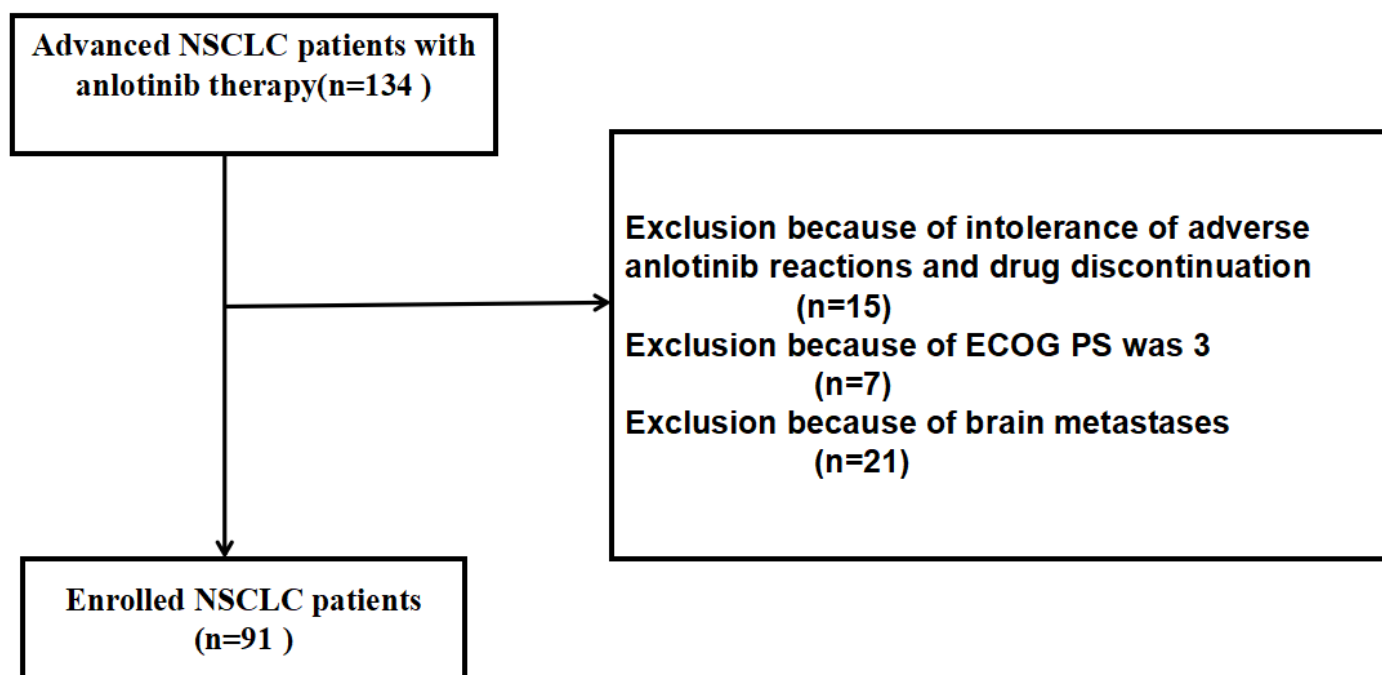


Figure 1

consort diagram, enrollment and outcome.

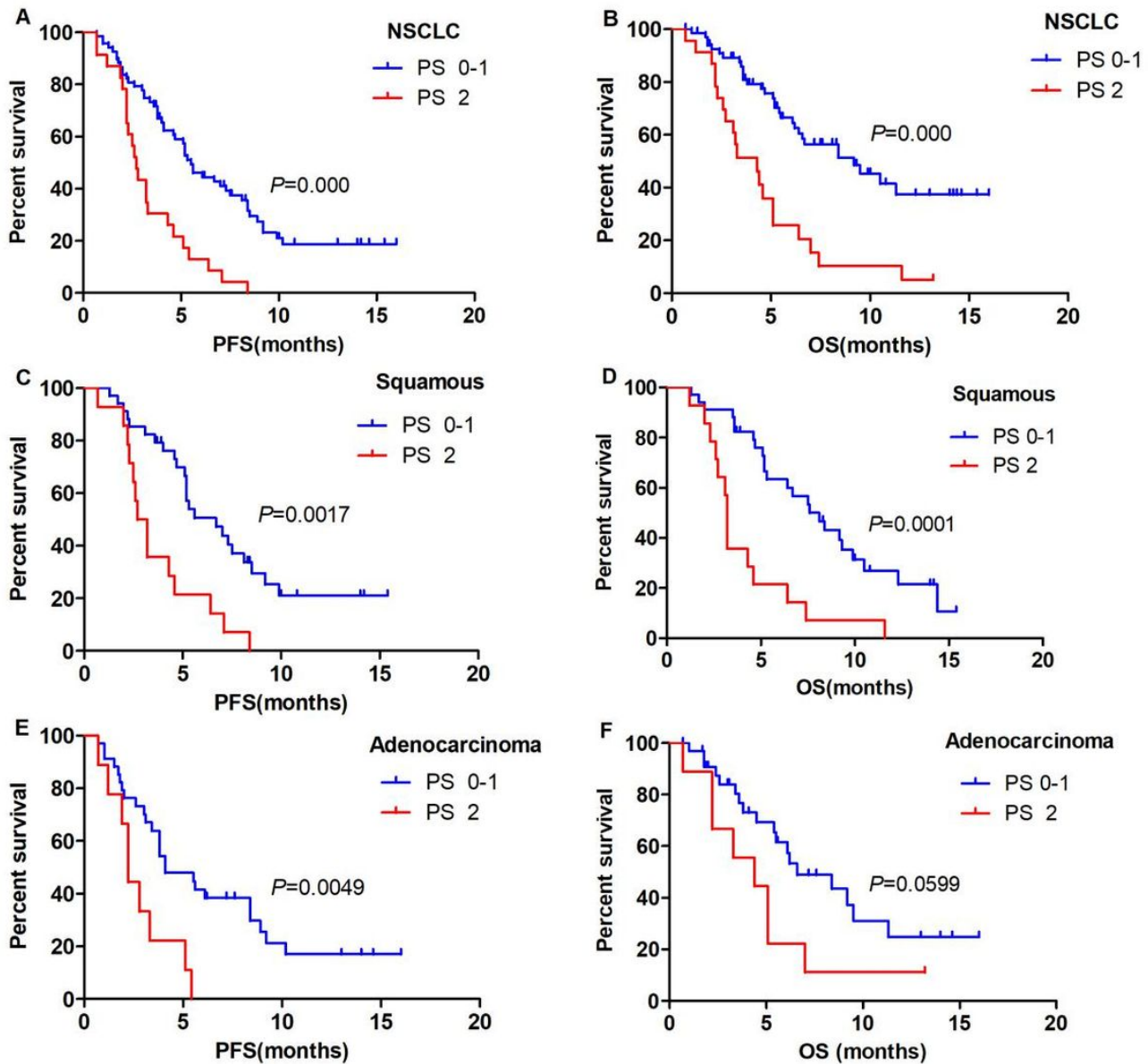


Figure 2

Efficacy results after the administration of anlotinib. PFS and OS: (A-B) PFS and OS Curves for ECOG PS and NSCLC; (C-D) PFS and OS Curves for ECOG PS and squamous; (E-F) PFS and OS Curves for ECOG PS and adenocarcinoma.