

Anlotinib versus Chemotherapy as a Third-line or Further Treatment for Advanced Small Cell Lung Cancer

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Research

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Abstract

Purpose The optimal third-line or further treatment for advanced small cell lung cancer (SCLC) remains unclear. Anlotinib, which is a novel multitarget tyrosine kinase inhibitor, could inhibit tumor angiogenesis and proliferative signaling. This retrospective study aimed to compare the efficacy and safety of anlotinib versus chemotherapy of patients with advanced SCLC progressing after second-line or further treatment.

Methods This study included 55 advanced SCLC patients (n=28 for anlotinib group and n=27 for chemotherapy group) from Shanghai Chest hospital between January 2017 and September 2019. Detailed demographic, survival data, and safety data were collected. Kaplan-Meier method and log-rank test were used to assess median progression-free survival (PFS) and overall survival (OS) with 95% confidence intervals (CIs).

Results PFS was significantly longer in the anlotinib group [median PFS 3.58 versus 2.56 months; hazard ratio (HR)=0.42, 95% CI:0.24-0.75, P=0.003] than that in the chemotherapy group. Although anlotinib did not improve OS (median OS 5.32 versus 6.57 months; HR=1.21, 95% CI:0.60-2.46, P=0.592), non-smokers derived more survival benefit from anlotinib than ever/current smokers ($P_{\text{interaction}}$ for OS=0.04). In addition, similar result was found for PFS ($P_{\text{interaction}}$ for PFS=0.08). Considerable improvement in disease control rate was observed in the anlotinib group over the chemotherapy group. Four (14.3%) patients in the anlotinib group versus five (18.5%) patients in the chemotherapy group had treatment-related grade 3-4 adverse events.

Conclusion Anlotinib treatment resulted in an improvement of PFS versus chemotherapy in previously treated SCLC, with a favourable safety profile. Non-smoking seemed to be a predictive factor of anlotinib efficacy. Prospective studies were needed to confirm our findings.

1 Introduction

Among all cancer types, lung cancer remains the leading cause of cancer-related death¹. Small cell lung cancer (SCLC), characterized by rapid doubling time and sensitivity to both chemotherapy and radiation, accounts for about 10%-20% of lung cancer^{2, 3}. Although SCLC is very sensitive to initial treatment, most patients

relapse with relatively resistant disease. Further systemic treatment can only bring these patients 4 to 5 months median survival⁴. The systemic therapy of advanced SCLC remains an urgent problem to be solved.

Several studies have proposed that inducing angiogenesis is one of a hallmark of cancer that leads to rapid tumor spread and metastasis^{5, 6}. Angiogenesis greatly contributes to the metastatic process of SCLC, which has a higher vascularization compared with non-small-cell lung cancer (NSCLC). A retrospective study of 87 patients with resected SCLC tumors treated with adjuvant chemotherapy showed that both microvessel count and VEGF expression were associated with worse overall

survival, suggesting that SCLC may be an ideal field to test new antiangiogenic drugs associated to chemotherapy⁷. Anlotinib, a new administered tyrosine kinase inhibitor developed by China, inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFR β and FGFR1⁸. In phase 2 of the ALTER1202 randomized clinical trial, 120 patients with advanced SCLC who progressed after second-line or further treatment were enrolled from 11 centers; 81 of these patients were assigned to the anlotinib arm and 38 patients to the placebo arm. The ALTER1202 trial showed that progression-free survival (PFS) was significantly longer in the anlotinib group (median PFS 4.1 versus 0.7 months) than that in the placebo group, reducing the risk of disease progression by 81%⁹. In addition, The ALTER 0303 trial—a phase 3 randomized clinical trial designed to evaluate the efficacy and safety of anlotinib in

patients with advanced NSCLC, showed anlotinib as third-line and further therapy is well tolerated and offers significantly improved PFS (median PFS 5.4 months versus 1.4 months; $P < 0.001$) and OS (median OS 9.6 versus 6.3 months; $P = 0.002$) compared with placebo among Chinese patients¹⁰. Guidelines of Chinese Society of Clinical Oncology (CSCO) have added anlotinib as third or further line treatment for NSCLC and SCLC. However, in real life, subsequent systemic therapy of advanced SCLC usually chose chemotherapy rather than placebo¹¹. Therefore, the purpose of our study was to assess the efficacy and safety of anlotinib versus chemotherapy as third or further line treatment for patients with advanced SCLC.

2 Material And Methods

2.1 Data source and patient selection

We retrospectively collected the medical data of SCLC patients who were treated at Shanghai Chest Hospital between January 2017 and September 2019. The study protocol was approved by the Ethics Committee of Shanghai Chest Hospital and was conducted in accordance with the Helsinki Declaration of 1964 (revised 2008). Inclusion criteria included as following: those aged 18–80 years who had histologically or cytologically confirmed SCLC; an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–2 (score range: 0–5, with the highest score indicating death); recurrent or advanced SCLC (stage IIIB, IIIC, or IV [American Joint Committee on Cancer Cancer Staging Manual, 8th edition]) with failure of at least two lines of treatment; adequate liver and kidney function; no myelosuppression and no driver alterations. Exclusion criteria included the following: a non small-cell lung cancer (NSCLC, including mixed NSCLC/SCLC); a history of massive hemoptysis, a bleeding tendency, uncontrolled hypertension and abnormal coagulation.

According to the patients who had been identified in the anlotinib group, we selected the SCLC patients receiving chemotherapy with similar age, gender, clinical stage and pathological type in a 1-to-1 ratio.

2.2 Treatment

Twenty-eight patients received anlotinib (one cycle of 12 mg/10 mg daily for 14 days, discontinued for 7 days, and repeated every 21 days). The other twenty-seven patients received the third-line chemotherapy

(the chemotherapy regimen and dose referred to the NCCN guidelines and were made by the clinicians depending on the situation). Treatment was continued until the last follow-up visit, Response Evaluation Criteria in Solid Tumors guidelines-defined disease progression, development of unacceptable toxic effects or death.

2.3 Assessments

Tumor assessment was performed using Response Evaluation Criteria in Solid Tumors version 1.1¹² by computed tomography (CT) scans, nuclear magnetic resonance imaging (MRI) or abdominal ultrasound at every 6–8 weeks during treatment. The cut off date was 10 October 2019. Adverse events were classified and graded according to Common Terminology Criteria for Adverse Events, version 4.0.

2.4 Statistical analysis

Comparisons of characteristics between patients who received anlotinib or chemotherapy were performed using the Pearson χ^2 , Continuity correction or Fisher exact for categorical variables. Two groups in PFS and overall survival (OS) were compared using a univariate Cox proportional hazards model without stratification, a stratified Cox model for subgroups and a multivariate Cox model including group as a covariate in the whole population. Median PFS were estimated using the Kaplan–Meier method. Interaction and stratified analysis were conducted according to age (≤ 60 and > 60 years), smoking status (nonsmoker and ever or current smoker), histology (SNEC and other NEC), clinical stage (I and II), with or without brain metastases and disease classification (resistant disease and sensitive disease). Objective response rate (ORR) and disease control rate (DCR) for each group were compared using Pearson χ^2 or Fisher exact test. All statistical analyses were performed using SPSS (version 23.0, IBM, Armonk, NY) or R software (version 3.6.1, <http://www.R-project.org>). All p values were two sided and a p value < 0.05 was considered statistically significant.

3 Results

3.1 Characteristics of patients

In this study, 28 patients received anlotinib [of whom 27 (96.4%) were male and 1 (3.6%) were female, with a median (range) age of 61 (50–68) years] and the other 27 patients received chemotherapy [of whom 25 (92.6%) were male and 2 (7.4%) were female, with a median (range) age of 60 (44–71) years]. Baseline demographics and disease characteristics were well balanced between the anlotinib and chemotherapy groups (Table 1)

Table 1 Differences between Anlotinib and Chemotherapy in Demographic and Baseline Characteristics.

NEC=neuroendocrine carcinoma; SCNEC=small cell neuroendocrine carcinoma

Characteristics	Anlotinib (n=28)	Chemotherapy (n=27)	P value
Age (years)			0.504
≤60	12 (42.9%)	14 (51.8%)	
>60	16 (57.1%)	13 (48.1%)	
Gender			0.974
Male	27 (96.4%)	25 (92.6%)	
Female	1 (3.6%)	2 (7.4%)	
Smoking status			0.589
Nonsmoker	8 (28.6%)	6 (22.2%)	
Even/current smoker	20 (71.4%)	21 (77.8%)	
NEC			
SCNEC	22 (78.6%)	26 (96.3%)	0.117
Others	6 (21.4%)	1 (3.7%)	
Clinical stage			1.000
IIIB	2 (7.1%)	2 (7.4%)	
IV	26 (92.9%)	25 (92.6%)	
Number of metastases			0.661
≤2	25 (89.3%)	22 (81.5%)	
>2	3 (10.7%)	5 (18.5%)	
Brain metastases			0.853
No	10 (35.7%)	9 (33.3%)	
Yes	18 (64.3%)	18 (66.7%)	
No. of previous treatment lines			0.111
2	24 (85.7%)	27 (100%)	
≥3	4 (14.3%)	0 (0.0%)	
Disease classification			0.485
Resistant disease	22 (78.6%)	19 (70.4%)	
Sensitive disease	6 (21.4%)	8 (29.6%)	

Most patients' first-line regimen was cisplatin or carboplatin combined with etoposide or surgery and the second-line regimen included cisplatin or carboplatin combined with docetaxel, etoposide or ifosfamide. The previous treatments of these patients are shown in Supplement 1.

3.2 Survival analysis of PFS and OS

Median duration of follow-up was 11.14 months (95% CI:9.89–12.38). PFS was significantly longer in the anlotinib group [median PFS 3.58 versus 2.56 months; hazard ratio (HR) = 0.42, 95% CI:0.24–0.75, P = 0.003] than that in the chemotherapy group (Fig. 1A). Although anlotinib did not improve OS (median OS 5.32 versus 6.57 months; HR = 1.21, 95% CI:0.60–2.46, P = 0.592), non-smokers derived more survival benefit from anlotinib than ever/current smokers ($P_{\text{interaction}}$ for OS = 0.04, Fig. 1B and 2).

3.3 Univariate and multivariate Cox regression analysis of factors associated with PFS and OS

The results of univariate cox regression analysis for PFS and OS were shown in Table 2

Table 2 Univariate and multivariate Cox regression analysis of factors associated with PFS and OS in the overall population.

NEC=neuroendocrine carcinoma; SCNEC=small cell neuroendocrine carcinoma; PFS=progression-free survival; OS=overall survival; HR=hazard ratio

Characteristics	Univariate analysis for PFS		Univariate analysis for OS	
	HR (95%CI)	P	HR (95%CI)	P
Group				
Anlotinib	0.423 (0.238-0.750)	0.003	1.208 (0.596-2.452)	0.592
Chemotherapy	1		1	
Age (years)				
≤60	1.044 (0.601-1.815)	0.878	1.250 (0.622-2.515)	0.531
>60	1		1	
Gender				
Male	0.477 (0.146-1.565)	0.222	0.508 (0.153-1.687)	0.269
Female	1		1	
Smoking status				
Nonsmoker	0.779 (0.405-1.497)	0.453	0.951 (0.287-3.145)	0.934
Even/current smoker	1		1	
NEC				
Others	1.205 (0.510-2.850)	0.671	0.898 (0.315-2.557)	0.840
SCNEC	1		1	
Clinical stage				
IIIB	1.694 (0.596-4.819)	0.323	1.130 (0.268-4.753)	0.868
IV	1		1	
Number of metastases				
≤2	1.423 (0.661-3.063)	0.367	1.164 (0.442-3.066)	0.758
>2	1		1	
Brain metastases				
No	1.363 (0.760-2.444)	0.299	1.546 (0.758-3.155)	0.231
Yes	1		1	
Number of previous treatment lines				
2	1.928 (0.588-6.328)	0.279	0.540 (0.125-2.328)	0.409
≥3	1		1	

Disease classification				
Resistant disease	1.119 (0.600-2.085)	0.724	1.576 (0.648-3.833)	0.316
Sensitive disease	1		1	

Anlotinib was significantly associated with longer PFS (HR = 0.42,95% CI:0.24–0.75,P = 0.003) but not for OS (HR = 1.21,95% CI:0.60–2.45,P = 0.592).

3.4 Subgroup analysis of PFS and OS

The hazard ratio favored anlotinib across most subgroups defined according to stratification factors and other baseline characteristics for PFS.Although anlotinib did not improve OS,non-smokers derived more survival benefit from anlotinib than ever or current smokers ($P_{\text{interaction}}$ for OS = 0.04).In addition,similar result was found for PFS ($P_{\text{interaction}}$ for PFS = 0.08) (Fig. 2).

3.5 Objective response rate and disease control rate

Two patients in anlotinib group received partial response and no patient received in chemotherapy group.Here,we exhibit a patient who shows partial response after two cycles of anlotinib (Fig. 4).The objective response rate (14% vs 0%; P = 0.491) and disease control rate (60.7% vs 48.1%; P = 0.349) were higher in the anlotinib group compared with the chemotherapy group (Fig. 3).

3.6 Adverse events

Adverse events (AEs) observed in the anlotinib and chemotherapy group were showed in Supplement 2.Compared to the AEs associated with anlotinib reported in previous studies, no new AEs were observed in the present study¹³.Only two patients discontinued due to grade 3–4 hand-foot skin reaction and fatigue among the 28 small cell lung cancer patients.All hypertension caused by anlotinib can be effectively controlled by taking antihypertensive drugs and hand-foot skin reaction can also be relieved by reduction or other protective measures.We also tested the prognostic and predictive role of adverse events for anlotinib.We found that patients with adverse events had marginally PFS benefit from anlotinib ($P_{\text{interaction}}$ for PFS = 0.08). (Fig. 2).

4 Discussion

In this retrospective study,we summarized the clinical data of advanced SCLC patients at our hospital who received anlotinib or chemotherapy as their third-line or further treatment.Our results showed that anlotinib could provide significance PFS benefits in advanced SCLC.Although anlotinib did not improve OS,non-smokers derived more survival benefit from anlotinib than ever/current smokers.In addition,similar result was found for PFS.Anlotinib and chemotherapy had similar probability of grade 3–4 adverse events.

Several reasons may explain why anlotinib could receive better efficiency than chemotherapy. On the one hand, angiogenesis greatly contributes to the metastatic process of SCLC and anlotinib could inhibit angiogenesis via suppressing the activation of VEGFR2, PDGFR β and FGFR. As we have known, vascular endothelial growth factor (VEGF), one of the most important pro-angiogenic factors, is expressed by in vast majority of cancers, especially VEGFA^{14, 15}. Therefore, small cell lung cancer can benefit from anlotinib. Furthermore, compared to other anti-angiogenesis drugs, anlotinib is a multi-target drug, the scope of action of which is wider than that of a single target drug, and it is not easily resistant. Single medicine can be effective^{8, 16, 17}. On the other hand, the main reason for chemotherapy treatment failure in SCLC is intrinsic and acquired drug resistance. At present, the known drug resistance mechanisms in SCLC include overexpression of multidrug resistance (MDR) related proteins; abnormal expression of intracellular enzyme systems; apoptosis escape; abnormality of cell repair systems; cancer stem cells and so on¹⁸. These resistance mechanisms may not work for antiangiogenic drugs such as anlotinib.

The PFS of anlotinib versus chemotherapy was well sustained over the study period, but longer follow-up is required to ascertain the OS benefit in patients who responded to anlotinib. However, we found that in the chemotherapy group, many patients chose anlotinib as a subsequent treatment after resistance.

In the present study, nonsmoking seemed to be a predictor of high effectiveness with regard to anlotinib treatment in SCLC. Several studies have proved that tobacco smoking increases burden of somatic mutations and hence an elevated chance of acquiring “driver” mutations in cancer genes by the misreplication of DNA damage^{19, 20}. At the same time, patients with high tumor mutation burden associated with poor clinical outcomes in lung cancer treated with tyrosine kinase inhibitors (TKI) and anlotinib^{21–23}.

Our study has some limitations. First, it is a retrospective study. Selection bias may have affected our conclusions. Second, the sample size is a little small. Third, since there is no uniform standard for third or further line treatment of small cell lung cancer, most patients received chemotherapy, we set chemotherapy as the control group and there's no fixed chemotherapy regimen.

In conclusion, anlotinib treatment resulted in an improvement of PFS versus chemotherapy in previously treated SCLC, with a favourable safety profile. Non-smoking seemed to be a predictive factor of anlotinib efficacy. Prospective studies were needed to confirm our findings.

Declarations

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Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval This study was approved by the ethics committee and institutional review board of the Shanghai Chest Hospital and carried out in accordance with the declaration of Helsinki.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The data that support the findings of this study are available from the corresponding author upon request.

Code availability Not applicable.

Authors' contributions Conceptualization of the study was achieved by HZ, YW and XXYL. The research methodology was designed by WN and YW. Formal analysis of the data was conducted by WN, SHC and JWL. Project administration was carried out by HZ and WN. The study resources were obtained by JWL and YZ. Software analysis of data and figures was conducted by WN and SHC. In addition, supervision of the research was conducted by HZ and WN. Writing the manuscript was carried out by YW and WN. Review and editing of the manuscript were carried out by HZ.

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Figures

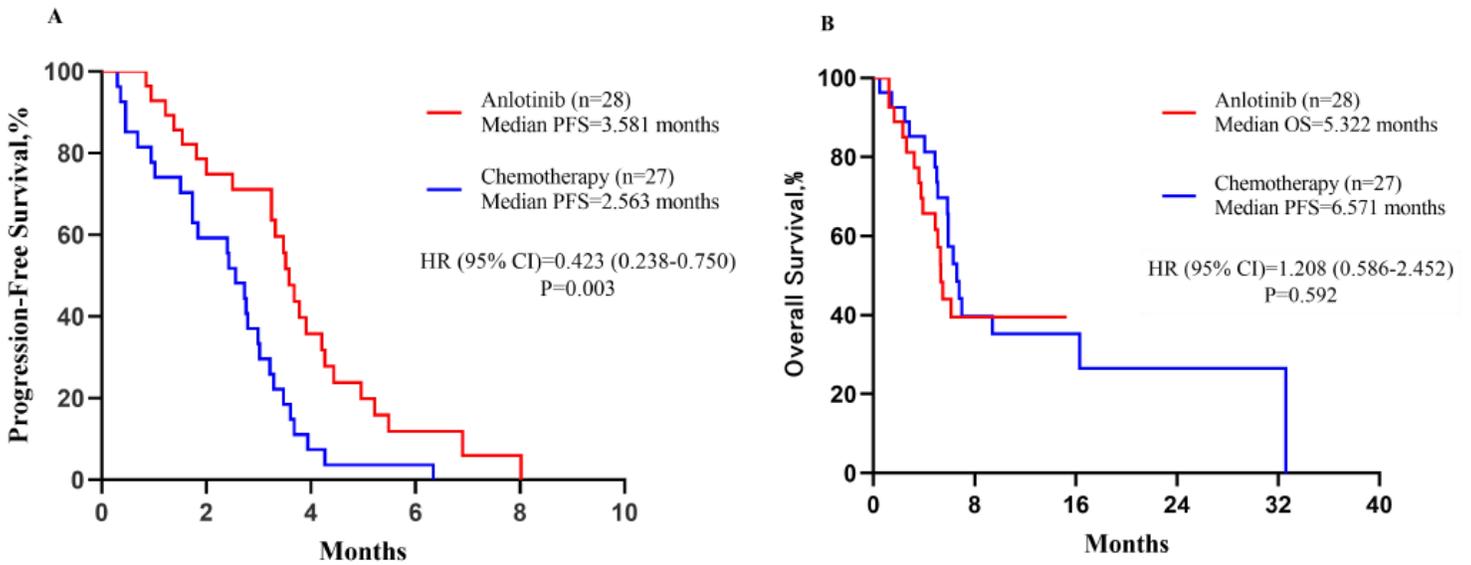


Figure 1

A.Kaplan-Meier Estimates of Progression-Free Survival B.Overall Survival. PFS=progression-free survival;OS=overall survival

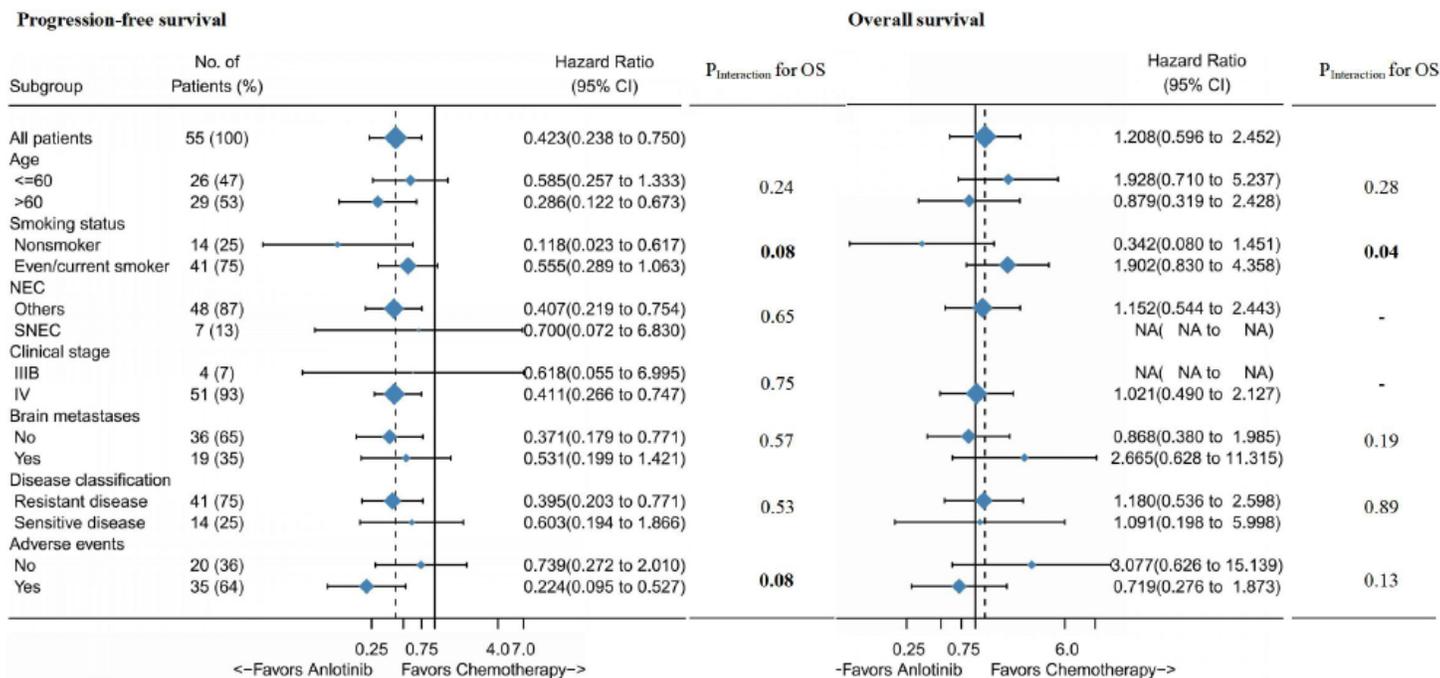


Figure 2

Subgroup Analysis of Progression-Free Survival and Overall Survival NEC=neuroendocrine carcinoma; SCNEC=small cell neuroendocrine carcinoma

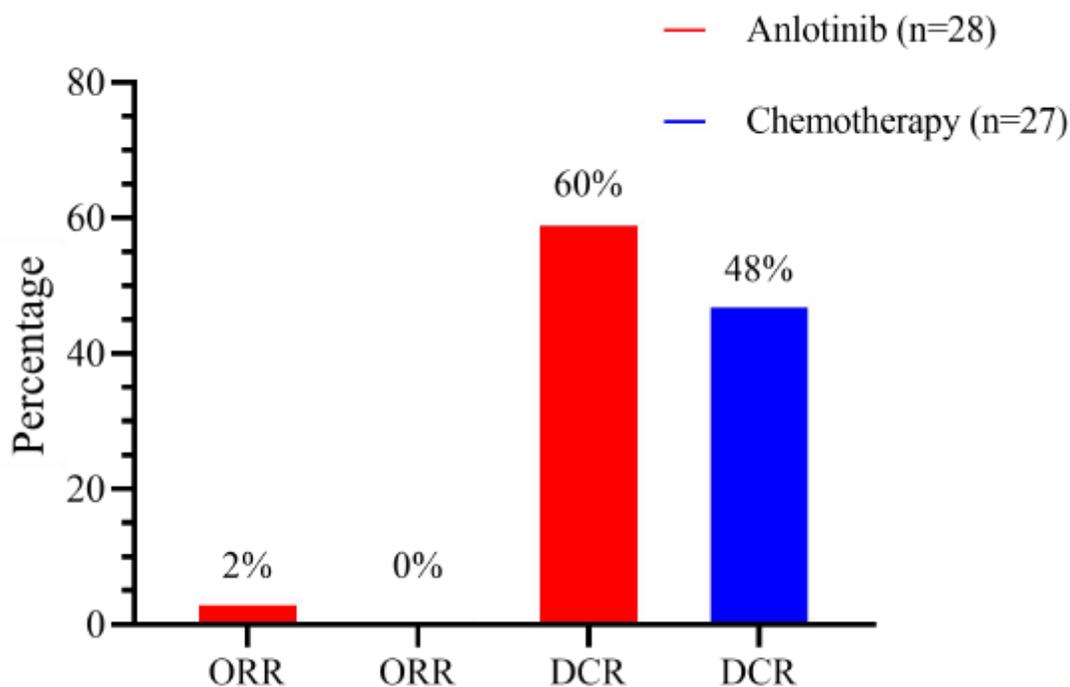
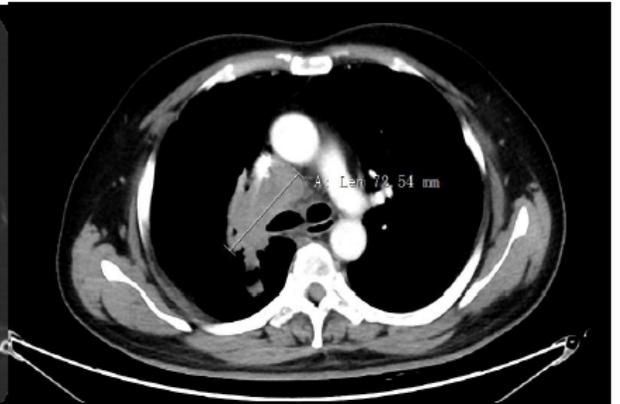
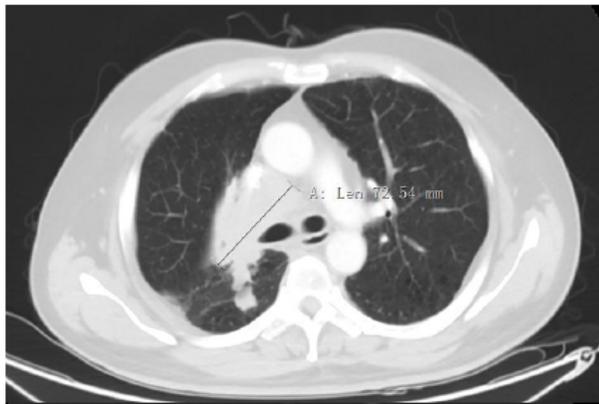


Figure 3

2018-10-22
A



2019-01-02
B



Figure 4

The Computed Tomography Images Exhibit a Patient with Advanced Small-cell Lung Cancer Shows Partial Response to Anlotinib.(A)Baseline assessment before anlotinib.(B)The tumor decreased after 6 weeks of anlotinib.

Supplementary Files

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