Oncology and Translational Medicine
DOI 10.1007/s10330-019-0370-0
February 2020, Vol. 6, No. 1, P10–P15

ORIGINAL ARTICLE

Efficacy and safety of anlotinib plus S-1 as thirdly-line or later-line treatment in advanced non-small cell lung cancer*

Heng Cao[1], Kai Liang (Co-first author)[2], Peng Liu (Co-first author)[2], Jing Wang[1], Yuanyuan Ji[1], Lujuan Xu[1], Weilong Wu[1], Shengnan Guo[1], Xuekun Song[3], Yonggui Hong[1] (✉)

[1] Department of Oncology, Anyang Tumor Hospital, The Fourth Affiliated Hospital of Henan University of Science and Technology, Anyang 455000, China
[2] Department of Surgical Oncology, Anyang Tumor Hospital, The Fourth Affiliated Hospital of Henan University of Science and Technology, Anyang 455000, China
[3] Henan University of Chinese Medicine, Zhengzhou 450000, China

Abstract

Objective Anlotinib, an oral vascular endothelial growth factor receptor 2 (VEGFR2) inhibitor, has confirmed antitumor activity in lung cancer in both *in vitro* and *in vivo* assays, and has been recommended as third-line treatment agent in non-oncogene driven non-small cell lung cancer (NSCLC). This prospective study aimed to investigate the efficacy and safety of anlotinib plus S-1 for third- or later-line treatment in patients with advanced NSCLC.

Methods Patients with histologically or cytologically confirmed NSCLC, and documented disease progression following second-line chemotherapy, and/or epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment were enrolled in this study. The patients were treated anlotinib (8 mg daily d 1–14) and S-1 (60 mg/m^2 d 1–14) and the treatment was repeated every 3 weeks. Treatment was continued until disease progression or unacceptable toxicity occurred. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and adverse events (AEs) were reviewed and evaluated.

Results Forty-one patients were enrolled in the study between June 2018 and December 2018. The total ORR and DCR were 26.8% and 80.5%, respectively. The median PFS was 5.2 months [95% confidence interval (CI), 3.9 to 6.6 months]. In the univariate analysis, there was a significant difference in the median PFS between patients with brain metastases and those without brain metastases (4.8 months vs 5.9 months, respectively; $P = 0.039$). The Eastern Cooperative Oncology Group (ECOG) performance status ($P = 0.002$), lines of therapy ($P = 0.015$), and therapeutic evaluation ($P = 0.014$) were independent factors that influenced PFS. The most common AEs were hypertension, proteinuria, myelosuppression, gastrointestinal reactions, fatigue, and mucositis.

Conclusion Anlotinib plus S-1 is an effective and safe regimen for advanced NSCLC as third- or later-line therapy.

Key words: non-small cell lung cancer (NSCLC); anlotinib; tegafur gimerac; advanced stage

Received: 23 July 2019
Revised: 25 August 2019
Accepted: 30 November 2019

Non-small cell lung cancer (NSCLC) is the leading cause of cancer morbidity and mortality wordwide [1]. Approximately 85% of lung cancers diagnosed are NSCLC, and more than half of the newly diagnosed patients present with metastatic disease [2]. The tyrosine kinase inhibitors (TKIs), such as gefitinib, afatinib, and erlotinib, are recommended as first-line therapy for advanced NSCLC patients harboring EGFR mutations [3]. However, for the majority of the advanced NSCLC patients without identifiable oncogenic drivers, platinum-doublet chemotherapy is the first-line treatment [4]. However, advanced NSCLC may be resistant to targeted- and

✉ Correspondece to: Yonggui Hong. Email: hygsir168@126.com
* Supported by a grant from the Youth National Science Foundation of China (No. 61702164).

chemotherapies, and second-line chemotherapy has poor efficacy with median survival time (MST) of less than 10 months [5]. Nivolumab, Pembrolizumab, and Atezolizumab are new candidates for use in second- or later-line therapies of advanced NSCLC [6]. Immunosuppressants have low efficiency and high cost for clinical therapeutic purposes, so their practical applications are limited. The optimization of the selection of treatment in advanced NSCLC after second- or above-line therapy has become a hot topic of research.

Vascular endothelial growth factor (VEGF) A was identified as the main mediator of angiogenesis. In addition, the high expression of VEGF contributes to cancer growth and metastasis by directly targeting the tumor cells [7–8]. Neutralizing monoclonal antibodies against VEGF and small molecule TKIs targeting VEGFRs are efficient methods to inhibit the angiogenic activity and metastasis of tumor [9]. Based on this theory, anti-angiogenic drugs, such as bevacizumab, have a place in the treatment of advanced NSCLC. Anlotinib, an oral VEGFR2 inhibitor, has confirmed antitumor activity in lung cancer *in vitro* and *in vivo*, and has been recommended as a third-line agent in advanced NSCLC without driver oncogenes [10]. Tegafur/gimeracil (trade name S-1), is composed of tegafur, gimeracil, and oteracil potassium. It has definite curative effects and controllable side effects in the treatment of advanced NSCLC [11]. This prospective study aimed to investigate the efficacy and safety of anlotinib plus S-1 as third- or later-line therapy in patients with advanced NSCLC.

Materials and methods

Patients

Between June 1st, 2018 and December 30th, 2018, 41 advanced NSCLC patients in the Anyang Tumor Hospital, the Fourth Affiliated Hospital of Henan University of Science and Technology, China, who failed more than second-line chemotherapy and/or EGFR-TKI treatment, were enrolled in the study and received anlotinib plus S-1 as third- or later-line treatment. All patients had been cytologically or histologically diagnosed with advanced NSCLC. Detailed variables of age, gender, smoking history, pathological type, metastasis sites, and other clinical data were obtained from electronic medical record system. Patients were treated anlotinib (8 mg daily d 1–14) and S-1 (60 mg/m^2 d 1–14) and the treatment was repeated every 3 weeks.

Therapeutic procedures

Treatment was interrupted or terminated under the following conditions: disease progression, serious adverse events (AEs), death of the patient, or voluntarily giving up. If grade 3 or 4 AEs occurred during anlotinib plus S-1 treatment, the treatment was initially suspended for 1–2 weeks to alleviate the side effects; and then, anlotinib plus S-1 treatment was continued. Treatment interruption and S-1 dose reduction (up to 1 dose; 40 mg/m^2) was permitted in case of drug-related AEs. If further dose reductions were required, then the patients were withdrawn from the study.

Efficacy and safety assessments

The patients followed the imaging requirements of the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Progression-free survival (PFS) was defined as the time from the first administration of anlotinib plus S-1 to the date of disease progression or occurrence of unacceptable toxicity. The last follow-up date was June 30th, 2019. Complete response (CR) was defined as the disappearance of all target lesions. Partial response (PR) was recorded when the longest diameter of target lesion reduced by at least 30%. Progressive disease (PD) was recorded when that the longest diameter of the target lesion increased by at least 20%, or the appearance of new lesions. Stable disease (SD) was recorded when the longest diameter of the target lesion increased to less than PD, or reduced to less than PR. Disease control rate (DCR) = (CR + PR + SD) / total number of cases × 100%, and the objective response rate (ORR) = (CR + PR) / total number of cases × 100%. AEs were determined using the National Cancer Institute Common Toxicity Criteria for AEs version 4.0.

Statistical analyses

PFS was assessed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analysis of the independent prognostic factors was evaluated using the Cox regression model. Statistical analyses were performed using SPSS version 21.0. $P < 0.05$ was considered to be statistically significant.

Results

Characteristics of patients

The demographic characteristics of 41 patients with advanced NSCLC are summarized in Table 1. The median age of the patients was 60 years, and there were 18 males and 23 females. Almost 51% of the patients had a favorable Eastern Cooperative Oncology Group (ECOG) performance status (0–1). A total of 23 patients received anlotinib plus S-1 as third-line therapy and 18 patients as further-line treatment. Thirty patients had adenocarcinoma and 11 had squamous cell carcinoma. Twelve patients presented with EGFR positive and 29 patients EGFR negative status. Nine patients had brain metastases. Thirteen patients had a previous smoking history, and 10 patients had a family history of cancer.

Table 1 Comparison of clinical efficacy according to different characteristics

Category	Number (%)	ORR	χ^2	*P*	DCR	χ^2	*P*
Gender							
Male	18 (43.9)	22.2	0.347	0.556	83.3	0.165	0.684
Female	23 (56.1)	30.4			78.3		
Pathological type							
Adenocarcinoma	30 (73.2)	26.7	0.002	0.969	80.0	0.017	0.896
Squamous carcinoma	11 (26.8)	27.3			81.8		
Age (years)							
≤ 65	24 (58.5)	29.2	0.161	0.688	83.3	0.209	0.585
> 65	17 (41.5)	23.5			76.5		
EGFR mutation							
Positive	12 (29.3)	41.7	1.903	0.168	75.0	0.325	0.568
Negative	29 (70.7)	20.7			82.8		
Smoking status							
Ever	13 (31.7)	23.1	0.137	0.712	84.6	0.207	0.650
Never	28 (68.3)	28.6			78.6		
Family history of cancer							
Yes	10 (24.4)	30.0	0.068	0.795	80.0	0.002	0.964
No	31 (75.6)	25.8			80.6		
Lines of therapy							
Thirdly-line	23 (56.1)	34.8	1.688	0.194	87.0	1.396	0.237
Later-line	18 (43.9)	16.7			72.2		
Brain metastases							
Yes	9 (22.0)	11.1	1.451	0.228	77.8	0.054	0.816
No	32 (78.0)	31.3			81.3		
ECOG							
0–1	21 (51.2)	38.1	2.783	0.095	85.7	0.749	0.387
2	20 (48.8)	15.0			75.0		

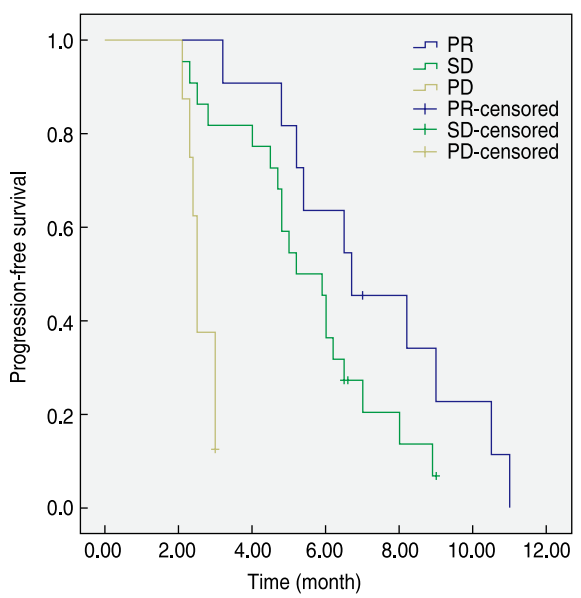

Fig. 1 The progression-free survival curves of NSCLC patients about therapeutic evaluation

Clinical efficacy

As shown in the waterfall plot (Fig. 1), none achieved a CR. Eleven patients obtained PR, 22 patients obtained SD, and 8 patients obtained PD. The ORR and DCR were 26.8% and 80.5%, respectively. The median PFS was 5.2 months (95% CI, 3.8 to 6.6 months).

Univariate and multivariate analyses

In univariate analysis (Table 2), patients with no brain metastases (P = 0.039), ECOG performance status 0–1 (P = 0.002), third-line of therapy (P = 0.015), and good therapeutic evaluation (P = 0.014) were associated with a longer PFS. However, in multivariate analysis (Table 2), patients with third-line of therapy (P = 0.015, HR = 0.383, 95% CI, 0.176 to 0.832), ECOG performance status 0–1 (P = 0.002, HR = 0.241, 95% CI, 0.098 to 0.593), PR *vs* PD (P = 0.005, HR = 0.124, 95% CI, 0.029 to 0.527), and SD *vs* PD (P = 0.006, HR = 0.127, 95% CI, 0.048 to 0.610) had significantly longer PFS.

Toxicity

Most adverse reactions were mild and controllable (Table 3). A total of 5 patients were followed-up until

Table 2 Progression-free survival of 41 NSCLC patients in univariate and multivariate analysis

Category	PFS (month)	*P*	
		Univariate	Multivariate
Gender			
Male	5.4 (3.9–6.9)	0.813	
Female	4.8 (3.8–5.8)		
Pathological type			
Adenocarcinoma	5.4 (4.4–6.4)	0.973	
Squamous carcinoma	4.7 (2.5–6.9)		
Age (years)			
≤ 65	5.4 (4.2–6.6)	0.920	
> 65	4.8 (2.1–7.5)		
EGFR mutation			
Positive	4.8 (0.1–10.2)	0.866	
Negative	5.2 (4.5–5.9)		
Smoking status			
Ever	5.2 (4.5–5.9)	0.730	
Never	5.2 (3.4–7.0)		
Family history of cancer			
Yes	4.8 (1.9–7.7)	0.488	
No	5.2 (4.4–6.0)		
Lines of therapy			0.015 (HR: 0.383,
Thirdly-line	6.2 (5.5–6.9)	0.012	95% CI: 0.176–0.832)
Later-line	4.5 (2.6–6.4)		1.00
Brain metastases			0.811 (HR: 1.115,
Yes	4.8 (3.2–6.5)	0.039	95% CI: 0.458–2.716)
No	5.9 (4.8–7.0)		1.00
ECOG			0.002 (HR: 0.241,
0–1	6.7 (5.3–8.1)	< 0.001	95% CI: 0.098–0.593)
2	4.0 (2.0–6.0)		1.00
Therapeutic evaluation			0.014
PR	6.7 (3.9–9.5)	< 0.001	0.005 (HR: 0.124, 95% CI: 0.029–0.527)
SD	5.2 (4.1–6.3)		0.006 (HR: 0.172, 95% CI: 0.048–0.610)
PD	2.5 (2.4–2.6)		1.00

Table 3 Toxicities during treatment (*n* = 41)

Adverse events	All grade (*n*)	Grade I–II	Grade III
Hypertension	18	15 (36.6%)	3 (7.3%)
Proteinuria	13	11 (26.8%)	2 (4.9%)
Gastrointestinal reactions	20	19 (46.3%)	1 (2.4%)
Fatigue	15	13 (31.7%)	2 (4.9%)
Myelosuppression	12	11 (26.8%)	1 (2.4%)
Mucositis	7	7 (17.1%)	
Hand-foot syndrome	7	5 (12.2%)	2 (4.9%)
Elevation of aminotransferase	6	6 (14.6%)	
Hemoptysis	2	2 (4.9%)	1 (2.4%)
Hypothyroidism	1	1 (2.4%)	

June 30th, 2019. One patient terminated the treatment due to unacceptable toxicity and associated hemoptyses. Three patients were treated with a reduced S-1 dose of 40 mg/m^2 d 1–14 due to development of myelosuppression and hand-foot syndrome. However, there was no reduction in the dosage of anlotinib during the treatment. The most common AEs of all levels were gastrointestinal reactions (48.8%), hypertension (43.9%), fatigue (36.6%), proteinuria (31.7%), myelosuppression (29.3%), mucositis (17.1%) and hand-foot syndrome (17.1%). The most frequently observed AEs of grade 3 were as follows: hypertension (7.3%), hand-foot syndrome (4.9%), proteinuria (4.9%), fatigue (4.9%), myelosuppression (2.4%), and hemoptyses (2.4%). No grade 4 AEs or treatment-related deaths were observed in this study.

Discussion

Angiogenesis is a crucial characteristics of cancer. The growth of new vessels is important to supply the growing malignant tumor with oxygen and nutrients [12]. VEGF and its receptors including VEGFR-1, VEGFR-2, and VEGFR-3 which cooperate to activate the signal transduction cascade in response to VEGF ligand binding, are often overexpressed in tumors. Hence, several different strategies have been designed to target the VEGF signal transduction [13]. In the last decade, multiple inhibitors have been therapeutically validated in preclinical models and clinical trials. Neutralizing monoclonal antibodies against VEGF and small molecule TKIs targeting VEGFRs have been shown to block its angiogenic activity, resulting in tumor vascular regression, antitumor effects, and improvements in patient survival, including bevacizumab [14], ramoluzzumab [15], endostar [16], anlotinib [10] among others.

Anlotinib is a potent multi-tyrosine kinases inhibitor (TKI) which inhibits the activation of VEGFR2, PDGFRβ, and FGFR1 and their common downstream ERK signaling [17]. It inhibits angiogenesis *in vitro* and *in vivo* by inhibiting VEGF/PDGF-BB/FGF-2. Alotinib is a potential agent for inhibiting angiogenesis and can be used in tumor therapy. In the phase III ALTER-0303 trial [10], 439 patients were randomized, 296 to the anlotinib group and 143 to the placebo group. PFS was significantly longer in the anlotinib group compared to the placebo group (5.4 months *vs* 1.4 months; HR = 0.25, 95% CI, 0.19 to 0.31; $P < 0.0001$). A substantial increase in OS was noted in the anlotinib group compared to the placebo group (9.6 months *vs* 6.3 months; HR = 0.70, 95% CI, 0.55 to 0.89; $P = 0.002$). These findings suggest that anlotinib is a potential third- or later-line therapy for patients with advanced NSCLC.

This is the first study to evaluate anlotinib plus S-1 as third- or later-line treatment in advanced NSCLC patients for its efficacy and safety. The results demonstrated the efficacy of anlotinib plus S-1 as shown by an ORR of 26.8%

and DCR of 80.5% in the 41 patients. The SD from our study demonstrated that the median PFS was 5.2 months, which was superior to that of single agent apatinib in the third-line setting. In phase II trial (ALTER0302) [18], PFS (4.8 months *vs* 1.2 months; HR = 0.32; 95% CI, 0.20 to 0.51; $P < 0.0001$), and ORR (10.0%; 95% CI, 2.4 to 17.6% *vs* 0%; 95% CI, 0 to 6.27%; $P = 0.028$) were better with anlotinib compared to the placebo. Currently, patients with brain metastases often receive radiotherapy. The median PFS of NSCLC patients with brain metastases was 3.0 to 3.7 months, and the median OS was only 7.4 to 12.2 months. Brain metastasis is one of the common and severe complications of lung cancer [19]. In this study, in the total of 9 patients with brain metastasis the data were as follows; PR (11.1%), SD (55.5%), PD (33.3%), and DCR was 66.6%. Within this subgroup, 5 patients had undergone brain radiotherapy before this study, including 4 patients with SD and 1 patient with PD, and the DCR was 80.0%. Four patients did not undergo any brain radiotherapy, including 1 patient with PR, 2 patients with SD, and 2 patients with PD, and the DCR was 60.0%. However, patients without brain metastases (HR = 0.421, 95% CI, 0.195 to 0.911; $P = 0.028$) had longer PFS following anlotinib treatment, which was different from the results of our study [20]. It would be interesting to determine whether brain radiotherapy combined with anlotinib plus S-1 improves the DCR of brain metastasis. However, further studies with larger sample size is needed to validate this observation. However, in multivariate analysis, patients with ECOG 0–1 vs ECOG 2 (6.7 months vs 4.0 months; HR = 0.241, 95% CI, 0.098 to 0.593; $P = 0.002$), third-line of therapy vs later-line of therapy (6.2 months *vs* 4.5 months; HR = 0.383, CI, 0.176 to 0.832; $P = 0.015$), PR *vs* PD (6.7 months *vs* 5.2 months; HR = 0.124, 95% CI, 0.029 to 0.527; $P = 0.005$), and SD *vs* PD (5.2 months *vs* 2.5 months; HR = 0.127, 95% CI, 0.048 to 0.610, $P = 0.006$) had significantly longer PFS, which were similar to the results from other studies [20–21]. The results of another study indicated that an ECOG PS of 0–1 (HR = 0.152, 95% CI, 0.057 to 0.403; $P = 0.001$) [20]. Based on the above, we concluded that parallel use TKIs and chemotherapy drugs increases PFS, especially in patients with good performance status.

The most frequent AEs included hypertension, proteinuria, myelosuppression, gastrointestinal reactions, fatigue, and mucositis. The overall incidence of grade 3 AEs was 29.3%. One patient with advanced NSCLC was terminated due to grade 3 hemoptysis, whose was cured after symptomatic treatment. Antivascular targeted therapy should be more carefully monitored in patients with hilar lung cancer or tumors that invade the central blood vessels. According to the AEs reported in the ALTER-0303 trial [22], the AEs observed in our study were expected of the treatment and could be controlled by intervention, and dose modification. No grade 4 AEs or treatment-related deaths were observed in this study.

In summary, anlotinib plus S-1 may be recommended as a third- or later-line therapy in advanced NSCLC patients due to its better efficacy and tolerable toxicity, especially in patients with good performance status. However, further studies are needed to define the clinical treatment strategies using anlotinib alone or in combination treatments such as when chemotherapy or immunosuppressants are used along with antivascular therapy.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin, 2018, 68: 7–30.
2. Ettinger DS, Akerley W, Borghaei H, *et al*. Non-small cell lung cancer. J Natl Compr Canc Netw, 2012,10: 1236–1271.
3. Sebastian M, Schmittel A, Reck M. First-line treatment of EGFR-mutated nonsmall cell lung cancer: critical review on study methodology. Eur Respir Rev, 2014, 23: 92–105.
4. Schiller JH, Harrington D, Belani CP, *et al*. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med, 2002, 346: 92–98.
5. Lima AB, Macedo LT, Sasse AD. Addition of bevacizumab to chemotherapy in advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS One, 2011, 6: e22681.
6. Passiglia F, Galvano A, Rizzo S, *et al*. Looking for the best immune-checkpoint inhibitor in pre-treated NSCLC patients: An indirect comparison between nivolumab, pembrolizumab and atezalizumab. Int J Cancer, 2018, 142: 1277–1284.
7. Kojima H, Shijubo N, Yamada G, *et al*. Clinical significance of vascular endothelial growth factor-C and vascular endothelial growth factor receptor 3 in patients with T1 lung adenocarcinoma. Cancer, 2005, 104: 1668–1677.
8. Takizawa H, Kondo K, Fujino H, *et al*. The balance of VEGF-C and VEGFR-3 mRNA is a predictor of lymph node metastasis in non-small cell lung cancer. Br J Cancer, 2006, 95: 75–79.
9. Sia D, Alsinet C, Newell P, *et al*. VEGF signaling in cancer treatment. Curr Pharm Des, 2014, 20: 2834–2842.
10. 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: 1569–1575.
11. Yumine K, Kawahara M. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Gan To Kagaku Ryoho (Japanese), 2006, 33 Suppl 1: 189–192.
12. Hoff PM, Machado KK. Role of angiogenesis in the pathogenesis of cancer. Cancer Treat Rev, 2012, 38: 825–833.
13. Shilpa P, Kaveri K, Salimath BP. Anti-metastatic action of anacardic acid targets VEGF-induced signaling pathways in epithelial to mesenchymal transition. Drug Discov Ther, 2015, 9: 53–65.
14. Gautschi O, Rothschild SI, Li Q, *et al*. Bevacizumab plus pemetrexed versus pemetrexed alone as maintenance therapy for patients with advanced nonsquamous non-small-cell lung cancer: Update from the

Swiss group for clinical cancer research (SAKK)19/09 trial. Clin Lung Cancer, 2017, 18: 303–309.
15. Garon EB, Ciuleanu TE, Arrieta O, *et al*. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet, 2014, 384: 665–673.
16. Zhou S, Zuo L, He X, *et al*. Efficacy and safety of rh-endostatin (Endostar) combined with pemetrexed/cisplatin followed by rh-endostatin plus pemetrexed maintenance in non-small cell lung cancer: A retrospective comparison with standard chemotherapy. Thorac Cancer, 2018, 9: 1354–1360.
17. Lin B, Song X, Yang D, *et al*. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRβ and FGFR1. Gene, 2018, 654: 77–86.
18. Han B, Li K, Zhao Y, *et al*. Anlotinib as a third-line therapy in patients with refractory advanced non-small-cell lung cancer: a multicentre, randomised phase II trial (ALTER0302). Br J Cancer, 2018, 118: 654–661.
19. Sun ZY, Chen Y. Updates in the management of brain (leptomeningeal) metastasis of lung cancer. Oncol Transl Med, 2018, 4: 144–150.
20. Wang J, Zhao Y, Wang Q, *et al*. Prognostic factors of refractory NSCLC patients receiving anlotinib hydrochloride as the third- or further-line treatment. Cancer Biol Med, 2018, 15: 443–451.
21. Wu D, Nie J, Dai L, *et al*. Salvage treatment with anlotinib for advanced non-small cell lung cancer. Thorac Cancer, 2019, 10: 1590–1596.
22. Si X, Zhang L, Wang H, *et al*. Management of anlotinib-related adverse events in patients with advanced non-small cell lung cancer: Experiences in ALTER-0303. Thorac Cancer, 2019, 10: 551–556.

DOI 10.1007/s10330-019-0370-0
Cite this article as: Cao H, Liang K, Liu P, *et al*. Efficacy and safety of anlotinib plus S-1 as thirdly-line or later-line treatment in advanced non-small cell lung cancer. Oncol Transl Med, 2020, 6: 10–15.