Effectiveness and Safety of Anlotinib Monotherapy for Patients with Extensive-stage Small-Cell Lung Cancer Who Progressed to Chemotherapy: A Real-world Exploratory Study

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ABSTRACT

BACKGROUND: Anlotinib demonstrated promising efficacy for patients with extensive-stage small-cell lung cancer (ES-SCLC) in clinical trials. However, the real-world evidence of anlotinib monotherapy in ES-SCLC was still limited currently. Therefore, present study was to investigate the effectiveness and safety of anlotinib for patients with ES-SCLC who progressed to chemotherapy in real-world and the potential biomarker during anlotinib monotherapy.

METHODS: A total of 89 patients with ES-SCLC who failed the previous chemotherapy treatment were recruited. All the patients were administered with anlotinib monotherapy. Demographic data of the patients were collected; effectiveness and safety profile during anlotinib monotherapy were documented through electronic medical record system in the hospital. Progression-free survival (PFS) and overall survival (OS) were presented using Kaplan-Meier survival curves and multivariate analysis was adjusted by Cox regression analysis.

RESULTS: All the 89 patients with ES-SCLC who progressed to chemotherapy were available for the assessment of effectiveness and safety profile. Best overall response indicated that partial response was observed in 6 patients (6.7%), stable disease was noted in 61 patients (68.5%), and progressive disease was found in 22 patients (24.7%). Therefore, the objective response rate (ORR) and disease control rate (DCR) of the 89 patients with ES-SCLC was 6.7% (95% confidence interval [CI]: 2.5%-14.1%) and 75.3% (95% CI: 65.0%-83.8%), respectively. The prognostic data suggested that the median PFS of the 89 patients was 3.1 months (95% CI: 2.10-4.10), and the median OS was 8.6 months (95% CI: 7.42-9.78). In addition, the most common adverse reactions of the patients who received anlotinib monotherapy were hypertension (34.8%), hand-foot syndrome (30.3%), fatigue (29.2%), loss of appetite (27.0%), and hematological toxicity (21.3%). Association analysis between biomarker (hypertension status) and prognosis indicated that the median PFS of patients with hypertension and patients without hypertension was 5.5 and 3.0 months, respectively ($\chi^2=4.64, P=0.031$). Furthermore, multivariate Cox analysis for PFS suggested that hypertension status was an independent factor for PFS (hazard ratio [HR] = 0.71, $P=0.035$).

CONCLUSION: Anlotinib monotherapy showed encouraging effectiveness and acceptable safety profile for patients with ES-SCLC in real world. Hypertension induced by anlotinib administration might be used as a potential biomarker to predict superior PFS for patients with ES-SCLC.

KEYWORDS: Small-cell lung cancer, effectiveness, safety, anlotinib, biomarker

Introduction

It is estimated that there are approximately 815 000 new cases and 715 000 new deaths of lung cancer in China annually.1 Small-cell lung cancer (SCLC) accounts for approximately 15% of lung cancers.2 Consequently, there are approximately 122 000 new cases and 107 000 death of SCLC in China each year.3 Although recent years had witnessed significant progress for the diagnostic techniques in SCLC, almost two-thirds of the patients were diagnosed with extensive-stage SCLC (ES-SCLC) according to the veteran affairs lung group staging criteria.4 Prognosis of patients with ES-SCLC was dismal with the 5-year survival rate <5% and median overall survival (OS) of 7-10 months.5 Although platinum and etoposide exhibited promising overall response in the first-line setting, considerable patients with ES-SCLC would relapse ultimately.6 Only a few drugs were available in second-line treatment for ES-SCLC. Topotecan was the standard-second-line therapeutic regimen.7 Unfortunately, the efficacy of topotecan was modest and hematologic toxicity was significant.8 It should be noted that PD-1/PD-L1 blockades exhibited dramatically clinical benefit for patients with different tumor types during the past years.9 Pembrolizumab and nivolumab were all available for ES-SCLC as third-line...
effective regimens recently. Although atezolizumab and durvalumab combined with chemotherapy demonstrated compelling efficacy for patients with ES-SCLC in the first-line setting according to Impower133 and CASPIAN clinical trials, overall response of PD-1/PD-L1 blockades monotherapy was disappointing clinically. Therefore, patients with ES-SCLC who progressed after the previous systemic chemotherapy were in urgent need of effective therapeutic regimens currently.

Angiogenesis played an important role in tumor proliferation and metastasis. Previous in vitro study indicated that majority of SCLC tumor tissues exhibited positive VEGF expression, which was associated with worse prognosis. Antiangiogenic targeted drugs were proved to show potential antitumor activity in the treatment for ES-SCLC. Bevacizumab was reported to provide the patients with approximately 1 month of progression-free survival (PFS) benefits in a phase III clinical trial, which was similar to the PFS benefits (approximately 1 month) that observed in the Impower133 clinical trial with the addition of atezolizumab. It should be noted that anlotinib was found to improve PFS and OS in a phase II clinical trial (ALTER1202) even the OS of patients who received anlotinib was not amazing numerically. As a result, anlotinib was licensed in 2019 by the National Medical Products Administration (NMPA) as the monotherapy for SCLC and was only available in China currently. To the best of our knowledge, overall response of antiangiogenic tyrosine kinase inhibitor (TKI) monotherapy was disappointing. Objective response rate (ORR) of antiangiogenic TKI monotherapy was less than 18% clinically. Therefore, it was necessary to investigate the biomarkers that could predict the clinical activity of antiangiogenic-targeted drugs currently.

Hypertension was the most common adverse reaction during anlotinib administration. Previous exploratory research indicated that elderly patients with adverse reaction of hypertension induced by anlotinib administration conferred superior PFS. Consequently, this study was to investigate the effectiveness and safety of anlotinib monotherapy for patients with ES-SCLC who progressed after the chemotherapy in real world and the prognostic significance according to hypertension status.

Patients and Methods
Design of present study

Given that anlotinib was licensed in China for 2.5 years and considerable patients with SCLC were treated with anlotinib monotherapy, present study was designed as a real-world retrospective study. Patients with ES-SCLC who progressed after the previous systemic chemotherapy in the department of thoracic surgery of affiliated hospital of Hebei university from June 2018 to October 2020 were enrolled. Therefore, our study was retrospective analysis of real-world patients who were treated with anlotinib and the eligibility criteria were considered as investigator-based predefined selection criteria.

Inclusion criteria were as follows: (1) histological diagnosis of SCLC with imaging staging of extensive stage; (2) aged ≥18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 score; (4) anlotinib monotherapy was administered for patients who progressed after the previous systemic chemotherapy. Both patients with platinum-sensitive and platinum-resistant were included; (5) at least one measurable target lesion according to RECIST 1.1 criteria. Exclusion criteria included the following: (1) uncontrolled or newly diagnosed brain metastases; (2) exposure to anlotinib or other antiangiogenic TKIs previously; (3) concomitant with another cancer or serious diseases; (4) effectiveness assessment data were not available. As illustrated in Figure 1, a total of 89 patients were included in this study. This study was approved by the ethics committee of affiliated hospital of Hebei university (approved number: KY-2020616). Written informed consent was signed by each enrolled patient according to the recommendations of the Declaration of Helsinki.

Anlotinib administration

Anlotinib was administered orally at an initial dosage of 12 or 10mg per day before breakfast for 2 weeks and discontinued for 1 week, every 3 weeks as 1 cycle. The treatment was continued until progression or intolerable adverse reactions. In addition, dosage reduction was permitted according to the tolerance of the patients.

Assessment of effectiveness and adverse reactions

Treatment response was evaluated using RECIST version 1.1 criteria according to the judgment of investigator. Target lesion in chest was used computed tomography (CT), target in other position was used CT or magnetic resonance imaging (MRI) for each patient before and after the administration of anlotinib. Target lesions were assessed every 2 cycles or when it was necessary in clinic (clinical symptoms of the patients were getting worse). In addition, safety profile was assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria. Hypertension was defined as either new-onset hypertension or worsening grade (CTCAE v4.03) from baseline in patients with the 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.

Follow-up

Patients were followed up regularly. Initial follow-up was performed when the patient received anlotinib therapy, and then, the date of disease progression could be clearly obtained through the electronic medical record system. For OS, follow-up was mainly carried out by telephone. Patients were followed up once a month and the death status was mainly inquired. The progression or death event must be validated by at least 2
colleagues independently. The last follow-up date of this study was January 13, 2021.

Statistical analysis

All analyses were statistically analyzed using SPSS version 25.0. Difference of variables according to hypertension status was analyzed using chi-square test and the Mann-Whitney U nonparametric test, respectively. Objective response rate and DCR were assessed according to the best overall response of each patient; ORR was the proportion of complete response (CR) and partial response (PR) in total patients, and DCR was the proportion of CR and PR and stable disease (SD) in total patients. Survival curves were drawn using Stata software to present PFS and OS according to the hypertension status. The survival difference was analyzed using log-rank test; PFS and OS were defined according to the previous study. Multivariate Cox regression analysis was constructed for PFS including the variables that were significant in univariate analysis; \( P < .05 \) was considered as statistical significance.

Results

Baseline characteristics

Baseline characteristics of 89 patients with previously treated ES-SCLC were shown in Table 1. The median age was 63 years (range: 21-81 years); 61 patients were male (68.5%). ECOG performance status of 0-1 score was observed in 51 patients (57.3%). Nonsmoker and former smoker/smoker were found in 17 and 72 patients, respectively. All of the patients were extensive stage. Platinum-sensitive and platinum-resistant were reported in 43 and 40 patients, respectively. Previous second-line treatment was observed in 64 patients. A total of 72 patients had a history of previous radiotherapy. Besides, 12 patients (13.5%) had received targeted drug previously; 11 patients had received PD-1/PD-L1 therapy previously. And the initial dosage of anlotinib with 12 and 10 mg was found in 78 and 11 patients, respectively. Patients with the history of hypertension were observed in 29 cases. The median systolic pressure level was 123 mm Hg (range: 95-139) and the median diastolic pressure level was 81 mmHg (range: 56-89). A total of 9 patients were of stable brain metastases.

Effectiveness of the patients who received anlotinib monotherapy

Objective response rate and DCR of the 89 patients who received anlotinib monotherapy were based on the best overall response during anlotinib treatment. No CR and PR were observed in 6 patients (6.7%), SD was noted in 61 patients (68.5%), and progressive disease was reported in 22 patients (24.7%). Consequently, ORR was 6.7% (95% confidence interval: 2.6-12.3%) and DCR was 68.5% (95% confidence interval: 61.6-75.6%).

Figure 1. Flow chart of the retrospective study of anlotinib in the treatment for patients with previously treated extensive-stage small-cell lung cancer. ECOG indicates Eastern Cooperative Oncology Group; SCLC, small-cell lung cancer.
Table 1. Baseline characteristics of the 89 patients with ES-SCLC according to hypertension status.

| CHARACTERISTICS | TOTAL PATIENTS (N=89, %) | HYPERTENSION STATUS | P |
|----------------|--------------------------|----------------------|---|
|                |                          | HYPERTENSION (N=31)  | NON-HYPERTENSION (N=58) | |
| Age            |                          |                      | .435 |
| Median (range) | 63 (21-81)               | 62 (25-79)           | 63 (21-81) |
| Sex            |                          |                      | .906 |
| Male           | 61 (68.5)                | 21 (67.7)            | 40 (69.0) |
| Female         | 28 (31.5)                | 10 (32.3)            | 18 (31.0) |
| ECOG score     |                          |                      | .915 |
| 0-1            | 51 (57.3)                | 18 (58.1)            | 33 (56.9) |
| 2              | 38 (42.7)                | 13 (41.9)            | 25 (43.1) |
| Smoking status |                          |                      | .602 |
| Non-smoker     | 17 (19.1)                | 5 (16.1)             | 12 (20.7) |
| Former smoker/smoker | 72 (80.9) | 26 (83.9)           | 46 (79.3) |
| Clinical stages (VALG) |              |                      | 1.000 |
| Extensive      | 89 (100.0)               | 31 (100.0)           | 58 (100.0) |
| Relapse type of first-line regimen |                      |                      | .997 |
| Platinum-sensitive | 43 (48.4)       | 15 (48.4)            | 28 (48.3) |
| Platinum-resistant | 40 (44.9)       | 14 (45.2)            | 26 (44.8) |
| NA             | 6 (6.7)                  | 2 (6.5)              | 4 (6.9) |
| Previous systemic treatment |                      |                      | .726 |
| Second line    | 64 (71.9)                | 23 (74.2)            | 41 (70.7) |
| Subsequent line | 25 (28.1)            | 8 (25.8)             | 17 (29.3) |
| History of previous radiotherapy |                      |                      | .602 |
| Yes            | 72 (80.9)                | 26 (83.9)            | 46 (79.3) |
| No             | 17 (19.1)                | 5 (16.1)             | 12 (20.7) |
| History of targeted drug therapy |                      |                      | .593 |
| Yes            | 12 (13.5)                | 5 (16.1)             | 7 (12.1) |
| No             | 77 (86.5)                | 26 (83.9)            | 51 (87.9) |
| History of PD-1/PD-L1 therapy |                      |                      | .909 |
| Yes            | 11 (12.4)                | 4 (12.9)             | 7 (12.1) |
| No             | 78 (87.6)                | 27 (87.1)            | 51 (87.9) |
| Initial dosage of anlotinib |                      |                      | .430 |
| 12mg           | 78 (87.6)                | 26 (83.9)            | 52 (89.7) |
| 10mg           | 11 (12.4)                | 5 (16.1)             | 6 (10.3) |
| History of hypertension |                      |                      | .169 |
| Yes            | 29 (32.6)                | 13 (41.9)            | 16 (27.6) |
| No             | 60 (67.4)                | 18 (58.1)            | 42 (72.4) |

(Continued)
interval [CI]: 2.5%-14.1%) and DCR was 75.3% (95% CI: 65.0%-83.8%). And the waterfall plot for change in target lesion of 89 patients with previously treated ES-SCLC was illustrated in Figure 2. Furthermore, the CT scans for target lesion of lymph node in 1 patient with ES-SCLC who underwent 2 cycles of anlotinib monotherapy were illustrated in Figure 3. The target lesions were significantly reduced after anlotinib administration.

**Prognosis of the patients who received anlotinib monotherapy**

Median follow-up duration of all patients from the date of enrollment to the date of data cut-off was 8.5 months (follow-up range: 1-20 months). A total of 81 patients were observed the PFS events or death events when the data cutoff. Therefore, the PFS data maturity was 91.0%. As shown in Figure 4, the median PFS of the 89 patients receiving anlotinib monotherapy was 3.1 months (95% CI: 2.10-4.10).

Univariate analysis for PFS according to baseline characteristic subgroups was performed in this study. As exhibited in Table 2, ECOG score was associated with PFS significantly in univariate analysis. The median PFS of patients with ECOG 0-1 score and patients with 2 score was 3.6 and 2.4 months, respectively ($P$ = .023). Interestingly, patients with platinum resistance had a trend for worse PFS compared with those with platinum sensitivity (median PFS: 2.7 vs 3.6 months, $P$ = .113). Besides, patients who were treated with 10 mg anlotinib also had a trend for worse PFS compared with those who were administered with 12 mg anlotinib. However, the difference was not statistically significant ($P$ = .338).

A total of 66 patients were observed the death events when the data cutoff. Consequently, the OS data maturity was 74.2%. As exhibited in Figure 4, the median OS of the 89 patients who

| CHARACTERISTICS                  | TOTAL PATIENTS (N=89, %) | HYPERTENSION STATUS | $P$  |
|----------------------------------|--------------------------|---------------------|------|
|                                  |                          | HYPERTENSION (N=31) | NON-HYPERTENSION (N=58) |
| Systolic pressure level (mmHg)  |                          |                     |      |
| Median (range)                   | 123 (95-139)             | 122 (95-138)        | 123 (95-139) | .536 |
| Diastolic pressure level (mmHg) |                          |                     |      |
| Median (range)                   | 81 (56-89)               | 81 (59-89)          | 81 (56-88)  | .617 |
| Brain metastases (stable status) |                          |                     |      |
| Yes                              | 9 (10.1)                 | 4 (12.9)            | 5 (8.6)  | .523 |
| No                               | 80 (89.9)                | 27 (87.1)           | 53 (91.4) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ES-SCLC, extensive-stage small cell lung cancer; NA, not available; VALG, veteran administration lung group.
received anlotinib monotherapy was 8.6 months (95% CI: 7.42-9.78).

Safety profile of the patients who received anlotinib monotherapy

The maximum toxicity during anlotinib administration was included in the analysis. Initial dosage of anlotinib with 12 or 10 mg was safety and tolerable. As exhibited in Table 3, the common adverse reactions of the patients with ES-SCLC during anlotinib monotherapy were hypertension (34.8%), hand-foot syndrome (30.3%), fatigue (29.2%), loss of appetite (27.0%), hematological toxicity (21.3%), hypertriglyceridemia (16.9%), diarrhea (15.7%), weight loss (14.6%), AST/ALT elevation (12.3%), proteinuria (11.2%), and hyponatremia (10.1%). Grade 3-4 adverse reactions were hypertension (9.0%), hand-foot syndrome (5.6%), fatigue (1.1%), loss of appetite (2.2%), hematological toxicity (2.2%) and hypertriglyceridemia (1.1%), AST/ALT elevation (1.1%) and hyponatremia (1.1%), respectively.

Patients with hypertension were found in 31 cases (34.8%) during anlotinib administration. As exhibited in Table 1, baseline characteristics of patients with hypertension and non-hypertension were comparable (P > .05). In addition, it should be noted that the median timing of the occurrence of hypertension was 6 days (range: 2-33 days) after the first dose of anlotinib administration.

Association between hypertension status and PFS

Given that hypertension was the most common adverse reaction and easy to monitor, the correlation analysis was performed between hypertension status and PFS. Therefore, PFS of 89 patients with ES-SCLC according to hypertension status was illustrated in Figure 5, and the median PFS of patients with hypertension and patients with non-hypertension was 5.5 months (95% CI: 0.16-10.84) and 3.0 months (95% CI: 2.66-3.34), respectively. And the difference was statistically significant ($\chi^2 = 4.64, P = .031$).
Table 2. Univariate analysis of PFS according to baseline characteristic subgroups.

| CHARACTERISTICS                                 | NO. OF PATIENTS | MEDIAN PFS (MONTHS) | 95% CI       | P     |
|-------------------------------------------------|-----------------|---------------------|--------------|-------|
| Age (Years)                                     |                 |                     |              |       |
| <63                                             | 42              | 3.3                 | 2.13-4.47    | .611  |
| ⩾63                                             | 47              | 3.1                 | 2.05-4.15    |       |
| Sex                                             |                 |                     |              |       |
| Male                                            | 61              | 2.8                 | 1.96-3.64    | .421  |
| Female                                          | 28              | 3.3                 | 1.92-4.68    |       |
| ECOG score                                      |                 |                     |              |       |
| 0-1                                             | 51              | 3.6                 | 3.09-4.11    | .023  |
| 2                                               | 38              | 2.4                 | 1.78-3.02    |       |
| Smoking status                                  |                 |                     |              |       |
| Non smoker                                      | 17              | 3.1                 | 1.98-4.22    | .782  |
| Former smoker/smoker                            | 72              | 3.1                 | 2.03-4.17    |       |
| Relapse type of first-line regimen              |                 |                     |              |       |
| Platinum-sensitive                              | 43              | 3.6                 | 2.31-4.89    | .113  |
| Platinum-resistant                              | 40              | 2.7                 | 1.64-3.76    |       |
| Previous systemic treatment                     |                 |                     |              |       |
| Second line                                     | 64              | 3.3                 | 1.97-4.63    | .515  |
| Further line                                    | 25              | 3.1                 | 2.03-4.17    |       |
| History of previous radiotherapy                |                 |                     |              |       |
| Yes                                             | 72              | 3.1                 | 1.98-4.22    | .433  |
| No                                              | 17              | 2.8                 | 1.55-4.05    |       |
| History of targeted drug therapy                |                 |                     |              |       |
| Yes                                             | 12              | 3.5                 | 2.14-4.86    | .347  |
| No                                              | 77              | 3.1                 | 2.08-4.12    |       |
| History of PD-1/PD-L1 therapy                   |                 |                     |              |       |
| Yes                                             | 11              | 3.9                 | 3.05-4.75    | .527  |
| No                                              | 78              | 3.0                 | 2.11-3.89    |       |
| Initial dosage of anlotinib                     |                 |                     |              |       |
| 12mg                                            | 78              | 3.3                 | 2.19-4.41    | .338  |
| 10mg                                            | 11              | 2.5                 | 1.67-3.33    |       |
| History of hypertension                         |                 |                     |              |       |
| Yes                                             | 29              | 3.5                 | 2.43-4.57    | .313  |
| No                                              | 60              | 2.9                 | 1.92-3.88    |       |
| Brain metastases (stable status)                |                 |                     |              |       |
| Yes                                             | 9               | 3.3                 | 2.18-4.42    | .619  |
| No                                              | 80              | 3.1                 | 2.18-4.02    |       |

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PFS, progression-free survival.
Furthermore, Cox regression model was introduced to perform the multivariate analysis, which was shown in Table 4. After the multivariate adjustment, hypertension status was still an independent factor for PFS (hazard ratio [HR] = 0.71, \( P = .035 \)). Interestingly, ECOG score was also an independent factor for PFS after multivariate adjustment (HR = 0.68, \( P = .031 \)). Therefore, all the 31 patients with any grade hypertension were associated with superior PFS.

**Table 3.** Safety profile of the 89 patients with ES-SCLC who received anlotinib monotherapy.

| ADVERSE REACTIONS       | TOTAL (NO., %) | GRADES 1-2 (NO., %) | GRADE ≥3 (NO., %) |
|-------------------------|----------------|---------------------|-------------------|
| Hypertension            | 31 (34.8)      | 23 (25.8)           | 8 (9.0)           |
| Hand-foot syndrome      | 27 (30.3)      | 22 (24.7)           | 5 (5.6)           |
| Fatigue                 | 26 (29.2)      | 25 (28.1)           | 1 (1.1)           |
| Loss of appetite        | 24 (27.0)      | 22 (24.7)           | 2 (2.2)           |
| Hematological toxicity  | 19 (21.3)      | 17 (19.1)           | 2 (2.2)           |
| Hypertriglyceridemia    | 15 (16.9)      | 14 (15.7)           | 1 (1.1)           |
| Diarrhea                | 14 (15.7)      | 14 (15.7)           | 0 (0.0)           |
| Weight loss             | 13 (14.6)      | 13 (14.6)           | 0 (0.0)           |
| AST/ALT elevation       | 11 (12.3)      | 10 (11.2)           | 1 (1.1)           |
| Proteinuria             | 10 (11.2)      | 10 (11.2)           | 0 (0.0)           |
| Hyponatremia            | 9 (10.1)       | 8 (9.0)             | 1 (1.1)           |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate amino transferase; ES-SCLC, extensive-stage small cell lung cancer.

**Figure 5.** Progression-free survival of the 89 patients with previously treated extensive-stage small-cell lung cancer who received anlotinib monotherapy according to hypertension status. CI indicates confidence interval; PFS, progression-free survival.

Furthermore, Cox regression model was introduced to perform the multivariate analysis, which was shown in Table 4. After the multivariate adjustment, hypertension status was still an independent factor for PFS (hazard ratio [HR] = 0.71, \( P = .035 \)). Interestingly, ECOG score was also an independent factor for PFS after multivariate adjustment (HR = 0.68, \( P = .031 \)). Therefore, all the 31 patients with any grade hypertension were associated with superior PFS.

**Discussion**

For the past 30 years, etoposide plus platinum chemotherapy regimens were widely accepted as the standard first-line therapy for SCLC. Although a high rate of response of the regimen was achieved, majority SCLC always relapsed inevitably.\(^{25}\) Fortunately, recent years witnessed that atezolizumab and durvalumab combined with platinum doublet chemotherapy exhibited promising efficacy and tolerable adverse reactions in the first-line setting for patients with ES-SCLC according to Impower133 and CASPIAN clinical trials, respectively.\(^{11,12}\) However, treatment as subsequent line for patients with previously treated ES-SCLC remained dismal.\(^{26}\) Although drugs with different mechanism of action were explored, the results were unsatisfactory.\(^{27}\) As a novel oral multi-target TKI, anlotinib demonstrated promising anticancer activity for SCLC in clinical trials.\(^{17}\)
Objective response rate of the 89 patients with ES-SCLC who received anlotinib monotherapy was 6.7%, DCR was 75.3% and the median PFS was 3.1 months, which was slightly lower than that in the ALTER1202 clinical trial (phase II clinical trial of anlotinib in ES-SCLC, patients received anlotinib therapy: ORR = 4.9%, DCR = 71.6% median PFS = 4.1 months). We speculated that the retrospective design of our study might contribute to the discrepancy between the 2 studies. To our knowledge, the adherence of patients in retrospective study was inferior to that in clinical trial. And similar results were found in the another retrospective studies regarding the efficacy of antiangiogenic targeted drug in non–small-cell lung cancer (NSCLC) and SCLC. In addition, the difference of ECOG performance status score accounted for 42.7% in our study, which was higher than that in ALTER1202 trial (4.9%). Furthermore, multivariate Cox results suggested that ECOG score was an independent factor for PFS. And the result was consistent with that of the previous study. Interestingly, a recent study initiated by Song PF and colleagues included a total of 79 elderly patients with ES-SCLC who were treated with anlotinib monotherapy and the conclusion demonstrated that the efficacy of anlotinib monotherapy for elderly patients with SCLC was satisfactory, which was consistent with the results in our study. In addition, a previous phase II clinical trial initiated by Wu and colleagues recruited 45 patients with relapsed SCLC who were treated with anlotinib monotherapy of 12 mg. And the ORR and median PFS were 11% and 4.1 months, respectively. Effectiveness data were similar with those in our study. However, the median PFS was longer than that in our study. The reason could be the explanation that we discussed above. From the objective view, it should be noted that the OS in our study was slightly longer than that in the 2 clinical trials (median OS: 8.6 vs 6.1 and 7.3 months). A potential explanation for this discrepancy could be the fact that considerable patients with brain metastases (36%) were included in the study of Wu et al. However, only 10.1% patients with stable brain metastases were included in our study. And 26% patients with brain metastases were included in ALTER1202 trial. Previous study suggested that patients with brain metastases were associated with worse prognosis. Furthermore, we speculated that another possible interpretation could be the license of PD-1/PD-L1 blockades since the approval of anlotinib in 2018. To our knowledge, PD-1/PD-L1 blockades were still useful for patients with previously treated ES-SCLC as third-line therapy. And it should be noted that a total of 11 patients were treated with PD-1/PD-L1 blockades previously in our study. Therefore, PD-1/PD-L1 blockades were also available for the patients when progressed after anlotinib administration, which provided the patients with survival benefits continuously.

Hypertension was one of the common adverse reactions in our study. And this finding was in line with the safety profile of ALTER1202 study. In addition, a recent retrospective study indicated that hypertension was also the most common adverse reaction for elderly patients (>60 years) with ES-SCLC who received anlotinib monotherapy. Besides, other adverse reactions were hand-foot syndrome, fatigue, loss of appetite, hematological toxicity, hypertriglyceridemia, diarrhea, weight loss, AST/ALT elevation, proteinuria, and hyponatremia, which were the common adverse reactions that found in the ALTER1202 study and the other retrospective study. In addition, a total of 11 patients were treated with anlotinib of 10 mg and no new adverse reactions were observed during the study, which suggested that both 12 and 10 mg of anlotinib was safety after anlotinib administration. The reason could be the license of PD-L1 blockades since the approval of anlotinib in 2018. To our knowledge, PD-L1 blockades were still useful for patients with previously treated ES-SCLC as third-line therapy. And it should be noted that a total of 11 patients were treated with PD-L1 blockades previously in our study. Therefore, PD-L1 blockades were also available for the patients when progressed after anlotinib administration, which provided the patients with survival benefits continuously.

Relevance analysis in our study indicated that hypertension could be used as a potential biomarker to predict PFS, which were consistent with the results of the previous retrospective studies. In addition, previous retrospective study investigated the association between hypertension and efficacy of patients with advanced NSCLC who were treated with bevacizumab, and the results indicated that hypertension was associated with prognosis of the patients, which was in accordance with that in our study as well. To our knowledge, hypertension...
was a common adverse reaction that occurred during the treatment of angiogenesis inhibitors. Unfortunately, the mechanisms underlying were not investigated thoroughly. Hypertension induced by angiogenesis inhibitors might result from the inherent host biology which caused the difference in VEGF/VEGFR blockades and served as a biomarker for the efficacy of angiogenesis inhibitors.38 Besides, it should be noted that patients who received anlotinib of 10 mg had a trend for worse PFS compared with those with 12 mg anlotinib therapy, even the difference was not statistically significant (P = .338). We speculated this might result from the fact that some patients with poor performance status stood a good chance to choose 10 mg anlotinib therapy according to the investigators’ decision. In view of the positive association between hypertension with PFS, we thought anlotinib of 12 mg could be better for the patients if they could tolerate it and active measures should be used to control hypertension rather than interruption of anlotinib therapy clinically. However, the conclusion in our study should be validated in large-scale prospective trials subsequently.

Limitations were observed in present study inevitably. Obviously, this study was designed as a retrospective study and some inherent bias (a selection bias and the potentially low quality of collected data as not case report form (CRF)-based and monitored for consistency) could not be avoided. Still and all, we thought present study was of clinical significance for the prognostic evaluation of patients with previously treated ES-SCLC who received anlotinib monotherapy.

Conclusions
Collectively, present retrospective study highlighted the real-world evidence regarding the potential effectiveness and tolerable safety profile of anlotinib for patients with previously treated ES-SCLC. Hypertension induced by anlotinib therapy could be used as a potential biomarker to predict the superior PFS for patients with ES-SCLC.

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Author Contributions
YL and ZS designed the study, performed the data of this study, and wrote this manuscript. WS collected the data and participated in the patients’ follow-up. HW and JZ guided the design of the study and supervised the results of the study. All authors participated in the reviewed of the manuscript and approved the final manuscript.

Ethical Approval
This study was approved by the ethics committee of affiliated hospital of Hebei University (approved number: KY-2020616).

Informed Consent
All patients in this study provided the written informed consent.

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REFERENCES
1. Xu K, Zhang C, Du Y, et al. Progress of exosomes in the diagnosis and treatment of stage 4 lung cancer. Biomed Pharmacother. 2021;134:111111.
2. Li J, Wang Y, Li J, Che G. Prognostic value of pretreatment D-dimer level in small-cell lung cancer: a meta-analysis. Technol Cancer Res Treat. 2021;20:1-7.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66:115-132.
4. Yang S, Zhang Z, Wang Q, Emerging therapies for small cell lung cancer. J Hematol Oncol. 2019;12:47.
5. Liu Y, Hu X, Jiang J, et al. A prospective study of apatinib in patients with extensive-stage small-cell lung cancer after failure of two or more lines of chemotherapy. Nanotechnol 2020;20:245-255.
6. Dömé M, Moran T, Isla D, et al. SEOM clinical guidelines for the treatment of small-cell lung cancer (SCLC) (2019). Clin Transl Oncol. 2020:22:245-255.
7. Wang S, Zimmermann S, Parikh K, Mansfield AS, Adjei AA. Current diagnosis and management of small-cell lung cancer. May Clin Proc. 2019;94:1562-1562.
8. Zhao Y, Wan B, Zhang T, et al. Irinotecan, topotecan, paclitaxel or docetaxel for second-line treatment of small cell lung cancer: a single-center retrospective study of efficacy comparison and prognosis analysis. Trans Lung Cancer Res. 2019;8:829-837.
9. Ruiz-Coeders R, Devine WP. Targeted therapy and checkpoint immunotherapy in Lung cancer. Surg Pathol Clin. 2013;10:37-53.
10. Konala VM, Madhira BR, Ashraf S, Graziano S. Use of immunotherapy in extensive-stage small cell lung cancer. Oncology. 2020;98:749-754.
11. Horn L, Mansfield AS, Szczęsna A, et al. First-line axetilozumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379:2220-2229.
12. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394:1929-1939.
13. Cantelmo AR, Dejos C, Kocher F, Hilbe W, Wolf D, Pincher A. Angiogenesis inhibition in non-small-cell lung cancer: a critical appraisal, basic concepts and updates from American Society for Clinical Oncology 2019. Curr Opin Oncol. 2020;32:44-53.
14. Dowell JE, Amirkhan RH, Lai WS, Frawley WH, Minna JD. Survival in small cell lung cancer is independent of tumor expression of VEGF and COX-2. Anti-cancer Res. 2004;24:2367-2373.
15. Li H, Liu Y, Liu X, Zhao D, Liu J, Cheng Y. A novel multi-target tyrosine kinase inhibitor anlotinib combined with irinotecan has in-vitro anti-tumor activity against human small-cell lung cancer. Anticancer Drugs. 2020;31:1057-1064.
16. Tiseo M, Boni L, Ambrosio P, et al. Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive disease small-cell lung cancer: the GOIRC-AIFA FARM-6FMFJM trial. J Clin Oncol. 2017;35:1285-1287.
17. Ying Cheng QW, Kai Li, et al. OA13.03 anlotinib as third-line or further-line treatment in relapsed SCLC: a multicentre, randomized, double-blind phase 2 trial. J Thorac Oncol. 2018;13:S531-S532.
18. Giltiz BJ, Moon J, Glisson BS, et al. Sorafenib in platinum-treated patients with extensive stage small cell lung cancer: a Southwest Oncology Group (SWOG 0435) phase II trial. J Thorac Oncol. 2010;5:1835-1840.
19. Schneider BJ, Gadgeel SM, Ramnath N, et al. Phase II trial of sunitinib maintenance therapy after platinum-based chemotherapy in patients with extensive-stage small cell lung cancer. J Thorac Oncol. 2011;6:1117-1120.
20. Liu X, Qin S, Wang Z, et al. Correction to: early presence of anti-angiogenesis-related adverse events as a potential biomarker of antitumor efficacy in metastatic gastric cancer patients treated with apatinib: a cohort study. J Hematol Oncol. 2018;11:5.
21. Song PF, Xu N, Li Q. Efficacy and 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.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:226-247.
23. Miller TP, Fisher BT, Gets KD, et al. Unintended consequences of evolution of the common terminology criteria for adverse events. *Pediatr Blood Cancer*. 2019;66:e27747.

24. Goodwin R, Ding K, Seymour L, et al. Treatment-emergent hypertension and outcomes in patients with advanced non-small-cell lung cancer receiving chemotherapy with or without the vascular endothelial growth factor receptor inhibitor cediranib: NCIC Clinical Trials Group Study BR24. *Ann Oncol*. 2010;21:2220-2226.

25. Stratigos M, Matikas A, Voutsina A, Mavroudis D, Georgoulas V. Targeting angiogenesis in small cell lung cancer. *Transl Lung Cancer Res*. 2016;5:389-400.

26. de Jong WK, ten Hacken NH, Groen HJ. Third-line chemotherapy for small cell lung cancer. *Lung Cancer*. 2006;52:339-342.

27. Morgensztern D, Besse B, Grellier L, et al. Efficacy and safety of rontalpizumab tesirine in third-line and beyond patients with DLL3-expressing, relapsed/refractory small-cell lung cancer: results from the phase II TRINITY study. *Clin Cancer Res*. 2019;25:6958-6966.

28. Song ZZ, Zhao LF, Zuo J, et al. Clinical outcomes and safety of apatinib mesylate in the treatment of advanced non-squamous non-small-cell lung cancer in patients who progressed after standard therapy and analysis of the KDR gene polymorphism. *Onco Targets Ther*. 2020;13:603-613.

29. Geng N, Ding CM, Liu ZK, Song S, Hu WX. Influence of VEGFR2 gene polymorphism on the clinical outcomes of apatinib for patients with chemotherapy-refractory extensive-stage SCLC: a real-world retrospective study. *Int J Clin Oncol*. 2021;26:670-683.

30. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer*. 2009;115:2721-2731.

31. Rades D, Motisi L, Veninga T, Conde-Moreno A, Cacicedo J, Schild SE. Predictors of outcomes and a scoring system for estimating survival in patients treated with radiotherapy for metastatic spinal cord compression from small-cell lung cancer. *Clin Lung Cancer*. 2019;20:322-329.

32. Wu D, Nie J, Hu W, et al. A phase II study of anlotinib in 45 patients with relapsed small cell lung cancer. *Int J Cancer*. 2020;147:3453-3460.

33. Reddy SP, Dowell JE, Pan E. Predictors of prognosis of synchronous brain metastases in small-cell lung cancer patients. *Clin Exp Metastasis*. 2020;37:531-539.

34. Huang W, Chen JJ, Xing R, Zeng YC. Combination therapy: future directions of immunotherapy in small cell lung cancer. *Transl Oncol*. 2021;14:100889.

35. Li H, Zeng J, Jin X, et al. Apatinib for chemotheraphy-refractory extensive-stage SCLC: a retrospective study. *Cancer Chemother Pharmacol*. 2019;83:1083-1090.

36. Fang XC, Huang W, Zhang YM, Zhang HT, Xie WF. Hypertension as a predictive biomarker in patients with advanced non-small-cell lung cancer treated with apatinib. *Onco Targets Ther*. 2019;12:985-992.

37. Dahlberg SE, Sandler AB, Brahmer JR, Schiller JH, Johnson DH. Clinical course of advanced non-small-cell lung cancer patients experiencing hypertension during treatment with bevacizumab in combination with carboplatin and paclitaxel on ECOG 4599. *J Clin Oncol*. 2010;28:949-954.

38. Sanidas E, Papadopoulos DP, Vellou M, et al. The role of angiogenesis inhibitors in hypertension: following “Ariadne’s Thread.” *Am J Hypertens*. 2018;31:961-969.