Original Article

Effectiveness and safety of anlotinib plus anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies as maintenance therapy after first-line chemotherapy combined with anti-PD-1/PD-L1 antibodies in extensive-stage small cell lung cancer: a real-world study

Pan Yang[#], Hu Luo[#], Lintao Zhao, Fu Xiong, Chunlan Tang

Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Army Medical University, Chongqing, China

Contributions: (I) Conception and design: C Tang, P Yang, H Luo; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Chunlan Tang, MD, PhD. Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Army Medical University, No. 30 Gaotan Yanzheng Street, Chongqing 400038, China. Email: chunlantangok@126.com.

Background: Currently, chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy is the preferred first-line treatment option for extensive-stage small cell lung cancer (ES-SCLC), but with limited overall survival (OS) and progression-free survival (PFS) benefits. The combination of anti-angiogenic drugs with immunotherapy has shown encouraging anti-tumor activity and tolerability, with some degree of overcoming immune resistance. This study aimed to evaluate the effectiveness and safety of anlotinib plus anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC.

Methods: Between June 2020 and December 2021, 12 patients with newly diagnosed ES-SCLC in the First Affiliated Hospital of Army Medical University were retrospectively analyzed. All patients without disease progression after 4–6 cycles of first-line platinum-containing chemotherapy plus anti-PD-1/PD-L1 antibodies received anlotinib (12 mg oral/day, days 1–14, followed by 1 week off, every 3 weeks per cycle) plus anti-PD-1/PD-L1 antibodies as maintenance therapy. Several patients underwent chest radiotherapy (intensity-modulated radiotherapy using a 6 MV X-ray) without disease progression before maintenance therapy. The effectiveness and safety of anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC were evaluated.

Results: The median follow-up time was 31.1 months. During first-line treatment (including maintenance therapy), one patient achieved a complete response, eight patients achieved a partial response (PR), and three patients had stable disease, with an objective response rate of 75.0% and a disease control rate of 100.0%. During maintenance therapy with anlotinib plus anti-PD-1/PD-L1 antibodies, 50.0% of patients achieved further lesion remission on the basis of the prior initial treatment, of which one patient achieved a PR. The median PFS was 13.6 [95% confidence interval (CI): 11.2–15.6] months, and the median OS was 19.5 (95% CI: 14.5–24.5) months. Treatment-related any grade and grade 3–4 adverse events (AEs) were reported in 100.0% and 58.3% of patients, respectively. No life-threatening AEs were observed. Grade 3–4 AEs included leukocytopenia (58.3%, 7/12), thrombocytopenia (33.3%, 4/12), nausea (33.3%, 4/12), anemia (16.7%, 2/12), and fatigue (8.3%, 1/12). All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis.

Conclusions: The combination of anlotinib with anti-PD-1/PD-L1 antibodies demonstrated encouraging effectiveness and safety in treating patients with ES-SCLC, suggesting that it may be a preferred option for

maintenance therapy after first-line chemotherapy combined with immunotherapy.

Keywords: Anlotinib; anti-programmed cell death 1/ligand 1 antibodies (anti-PD-1/PD-L1 antibodies); maintenance therapy; small cell lung cancer (SCLC)

Submitted Mar 11, 2024. Accepted for publication May 31, 2024. Published online Jul 05, 2024.
doi: 10.21037/jtd-24-394
View this article at: https://dx.doi.org/10.21037/jtd-24-394

Introduction

Small cell lung cancer (SCLC) originates from neuroendocrine cells in the lung epithelium and accounts for appropriately 15–20% of all lung cancer cases (1). Due to the high malignancy of SCLC and its rapid progression and early metastasis characteristics, most patients present with obvious signs of metastasis at the time of initial diagnosis, resulting in a poor prognosis (2). Data from 1983 to 2012 showed that the median overall survival (OS) of patients with SCLC was only 7 months, with a 5-year OS of only 1–2% (3). Based on the American Veterans Administration Lung Study Group (VALG) staging system, SCLC can be divided into limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) SCLC. The previous standard first-line treatment for patients with ES-SCLC was platinum-containing chemotherapy (carboplatin or cisplatin) combined with etoposide, with an objective response rate (ORR) of 60–65% and a median OS of approximately 10 months (4,5). In recent years, although immune maintenance therapy after first-line immune checkpoint inhibitors (ICIs) combined with carboplatin and etoposide has shown superior OS compared with chemotherapy alone, the progression-free survival (PFS) benefit is limited (6,7). In the real world, a domestic multicenter retrospective study investigated the effectiveness and safety of programmed cell death 1/ligand 1 (PD-1/PD-L1) combined chemotherapy in treating advanced SCLC, followed by immune maintenance therapy alone. The study involved 154 patients with extended PFS and OS (8). Moreover, the treatment options after disease relapse are extremely limited with a poor prognosis.

Highlight box

Key findings

- The combination of anlotinib with anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies proved to be a favorable choice for maintenance therapy following first-line chemotherapy in conjunction with immunotherapy.

What is known and what is new?

- Chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy is the preferred first-line treatment option for extensive-stage-small cell lung cancer (ES-SCLC), but with restricted therapeutic advantages.
- This study demonstrated that anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC could significantly prolong progression-free survival and overall survival with an acceptable safety profile.

What is the implication, and what should change now?

- The main limitation of this study was the small sample size. We will increase our sample size and follow up with more patients.

Abnormalities in the tumor vascular system are characterized by disordered, immature, disorganized, poorly perfused, and permeable vessels (9) and may be one of the mechanisms of immune resistance. It plays direct immunosuppressive roles, including inhibition of dendritic cells differentiation and maturation (10), reduction of T cell migration and tumor infiltration (11,12), induction or maintenance of regulatory T cells and myeloid-derived suppressor cells (13,14), recruitment of tumor-associated macrophages leading to T cell inactivation (15), up-regulation of PD-1 expression on T cells to induce T cell exhaustion (16), and direct inhibition of T cell proliferation and cytotoxic activity (17,18).

Numerous studies indicate that anti-angiogenic therapies targeting vascular endothelial growth factor (VEGF) or VEGF receptor-2 (VEGFR-2) can modulate the tumor immunosuppressive microenvironment and may help to reverse immune resistance (19-21). The combined blockade of PD-1 and VEGFR in mouse tumor models induces strong synergistic antitumor responses, such as inhibition of VEGF-A expression and thus reducing T cell exhaustion in tumors (16,22). Anlotinib is a multitarget tyrosine kinase inhibitor (TKI) with anti-angiogenic, anti-tumor growth, proliferation, and migration properties by targeting VEGFR 1–3, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and

stem cell growth factor receptor (c-Kit) (23). The ALTER 1202 trial assessed the anti-tumor activity of anlotinib as a third- or further-line treatment in patients with ES-SCLC. The results showed that anlotinib extended the median PFS by 3.4 months (P<0.0001) and reduced the risk of disease progression by 81% compared to placebo (24). Therefore, anlotinib has been approved as a third-line therapy for SCLC by National Medical Products Administration (NMPA). However, the safety and efficacy of first-line maintenance therapy with anlotinib and anti-PD-1/PD-L1 antibodies in ES-SCLC are still unknown. Thus, the retrospective study was conducted to evaluate the effectiveness and safety of anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with anti-PD-1/PD-L1 antibodies in ES-SCLC. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-394/rc).

Methods

Participants

Between June 2020 and December 2021, patients with newly diagnosed ES-SCLC in the Department of Respiratory and Critical Care Medicine, First Affiliated Hospital of Army Medical University were retrospectively analyzed. The main inclusion criteria included: (I) patients with histopathologically confirmed ES-SCLC according to the VALG staging system; (II) patients who did not receive systemic therapy for ES-SCLC; (III) the assessment of tumor effectiveness adhered to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; (IV) patients who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients who were complicated with other malignant tumors, serious infections, tuberculosis, or poor cardiopulmonary function were excluded from this study. This study was conducted following the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Army Medical University [No. (B)KY2023090]. Informed consent from patients was exempted from the ethical review due to the retrospective design.

Procedures

Patients without disease progression after 4–6 cycles of first-line platinum-containing chemotherapy plus anti-PD-1/PD-L1 antibodies received anlotinib (Chia-tai Tianqing Pharmaceutical Co., Ltd., Nanjing, China) plus anti-PD-1/PD-L1 antibodies as maintenance therapy. The anti-PD-1/PD-L1 antibodies included atezolizumab (F Hoffmann-La Roche Ltd., Kaiseraugs, Switzerland), durvalumab (AstraZeneca, London, England), tislelizumab (BeiGene Co., Ltd., Shanghai, China), and sintilimab (Innovent Biologics, Suzhou, China). The choice of anti-PD-1/PD-L1 antibodies was mainly based on the approved drug indications, enrollment in phase III clinical trials, patient willingness, and drug accessibility. Several patients underwent chest radiotherapy (intensity-modulated radiotherapy using a 6 MV X-ray) without disease progression before maintenance therapy. The use of chest radiotherapy was based on the 2020 Chinese Society of Clinical Oncology (CSCO) guidelines (25) for the diagnosis and treatment of SCLC and patient selection. Maintenance therapy was continued until the disease progression or unacceptable toxicity.

Data collection and outcomes assessment

The medical records of each patient were retrospectively collected, including patients' demographic characteristics, disease history, treatment history, laboratory test results, tumor biomarker levels, treatment modalities, efficacy, and safety. The primary endpoint was PFS. Secondary endpoints included OS, ORR, disease control rate (DCR), and safety. The tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST version 1.1. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0).

Statistical analysis

The categorical variables were expressed as percentages and numbers, while the continuous variables were presented as mean with standard deviation or median with range. The PFS and OS were estimated using the Kaplan-Meier method and expressed as a median with a 95% confidence interval (CI). The survival curve was generated using R Statistical Language (version 3.5.0). All statistical analyzes were performed using SPSS (version 27.0) software, and a P<0.05 was considered statistically significant.

Table 1 Baseline characteristics of the study population

Characteristics	Patients (n=12)
Age (years), median (range)	57.0 (35.0–72.0)
Sex, n (%)	
Male	10 (83.3)
Female	2 (16.7)
ECOG performance status, n (%)	
0–1	7 (58.3)
2	5 (41.7)
Smoking status, n (%)	
≥20 pack-years	9 (75.0)
<20 pack-years	3 (25.0)
Stage, n (%)	
III	9 (75.0)
IV	3 (25.0)
Liver metastasis, n (%)	
Yes	2 (16.7)
No	10 (83.3)
Metastasis sites, n (%)	
≤3	7 (58.3)
>3	5 (41.7)
Radiotherapy, n (%)	
Yes	9 (75.0)
No	3 (25.0)
Anti-PD-1 or PD-L1 antibodies, n (%)	
Atezolizumab	2 (16.7)
Durvalumab	4 (33.3)
Tislelizumab	4 (33.3)
Sintilimab	2 (16.7)

ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1.

Results

Patient and treatment

Between June 2020 and December 2021, 12 patients with newly diagnosed ES-SCLC were included in this study. The baseline demographic and clinical characteristics of patients are shown in *Table 1*. The majority of patients were male, with a male-to-female ratio of 5:1. The median age of the 12 patients was 57.0 (range, 35.0–72.0) years. Five (41.7%) patients were aged >60 years and nine (75.0%) patients had a smoking history of ≥20 pack-years. Nearly half of the patients (5/12, 41.7%) had more than three metastatic sites. The proportions of patients treated with anti-PD-1 antibodies (tislelizumab and sintilimab) and anti-PD-L1 antibodies (atezolizumab and durvalumab) were 50.0% and 50.0%, respectively. Nine patients (75.0%) underwent chest radiotherapy after chemotherapy combined with immunotherapy (*Table 1*).

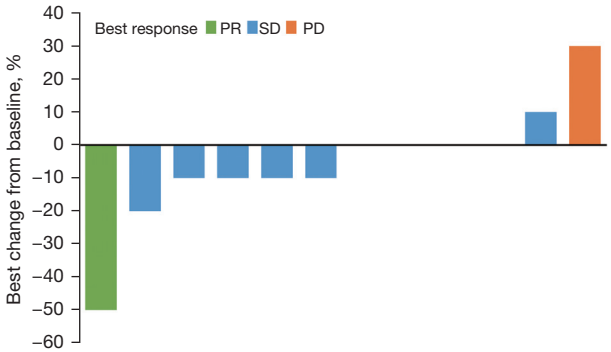

Figure 1 Assessment of the best percentage change from baseline in target lesion size from the time of maintenance therapy (n=12). PD, progressive disease; PR, partial response; SD, stable disease.

Efficacy

Up to the study cutoff date of May 11, 2023, the median follow-up time was 31.1 (95% CI: 14.8–47.5) months. During first-line treatment (including maintenance therapy), one patient achieved a CR, 8 patients achieved a PR, and three patients had SD, with an ORR of 75.0% and a DCR of 100.0%. During maintenance therapy with anlotinib plus anti-PD-1/PD-L1 antibodies, 50.0% of patients achieved further lesion remission on the basis of the prior initial treatment, of which one patient achieved a PR (*Figure 1*). The median PFS was 13.6 (95% CI: 11.2–15.6) months and the median OS was 19.5 (95% CI: 14.5–24.5) months (*Figure 2A,2B*). At the time of the last follow-up, 8 (66.7%) patients had died, and 4 (33.3%) patients were still alive with the longest OS of 32.7 months.

Safety

Treatment-related AEs of any grade were reported in 100.0% of patients, the majority of which were regarded

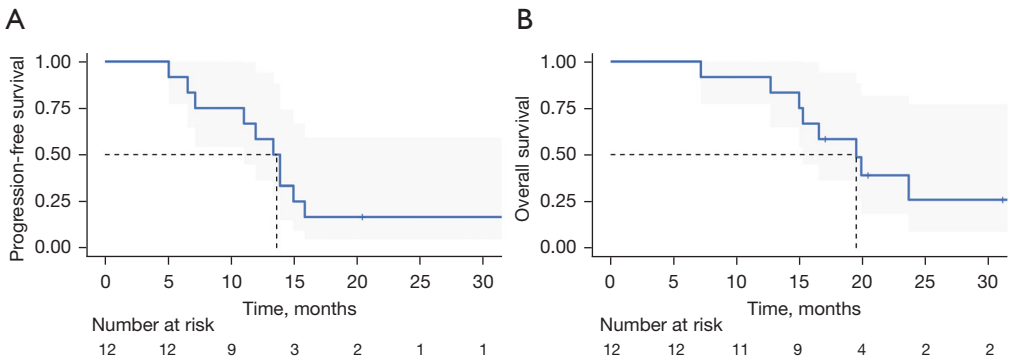

Figure 2 Patient survival curve. (A) Kaplan-Meier curve for progression-free survival. (B) Kaplan-Meier curve for overall survival.

Table 2 Treatment-related adverse events occurring in >10% of patients (n=12)

Adverse events	All grades, n (%)	Grades 1–2, n (%)	Grades 3–4, n (%)
Any	12 (100.0)	5 (41.7)	7 (58.3)
Fatigue	11 (91.7)	10 (83.3)	1 (8.3)
Radiation pneumonitis	9 (75.0)	9 (75.0)	0
Leukocytopenia	11 (91.7)	4 (33.3)	7 (58.3)
Thrombocytopenia	8 (66.7)	4 (33.3)	4 (33.3)
Anemia	11 (91.7)	9 (75.0)	2 (16.7)
Nausea	8 (66.7)	4 (33.3)	4 (33.3)
Hand-foot syndrome	2 (16.7)	2 (16.7)	0
Hypothyroidism	1 (8.3)	1 (8.3)	0
Diarrhoea	1 (8.3)	1 (8.3)	0

as grade 1–2 (*Table 2*). Seven (58.3%) patients experienced grade 3–4 treatment-related AEs. No life-threatening AEs were observed. Grade 3–4 AEs (*Table 2*) included leukocytopenia (58.3%, 7/12), thrombocytopenia (33.3%, 4/12), nausea (33.3%, 4/12), anemia (16.7%, 2/12), and fatigue (8.3%, 1/12). All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis.

Discussion

Currently, there is no standard first-line maintenance treatment regimen for ES-SCLC. Although chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy is the preferred first-line treatment option for ES-SCLC, the OS and PFS benefits are limited. The present study evaluated the effectiveness and safety of anlotinib plus immunotherapy as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC. The median PFS and OS of our patients were 13.6 (95% CI: 11.2–15.6) months and 19.5 (95% CI: 14.5–24.5) months, respectively, which were higher than those reported from chemotherapy plus immunotherapy followed by maintenance therapy with immune monotherapy. All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis. Besides, no patients occurred treatment interruption due to AEs. These findings suggested that anlotinib plus immunotherapy might be a preferable first-line maintenance treatment option for ES-SCLC.

The IMPOWER-133, CASPIAN, ASTRUM-005, and CAPSTONE-1 trials demonstrated that adding anti-PD-1/PD-L1 antibodies to chemotherapy improved the OS of patients with ES-SCLC compared with

chemotherapy alone, providing novel prospects for first-line treatment of patients with this disease. However, the immunotherapy combined with chemotherapy in the IMPOWER-133 (atezolizumab), CASPIAN (durvalumab), and CAPSTONE-1 [adebrelimab (SHR-1316)] (26) trials only extended the median OS by 2.0–2.5 months compared to chemotherapy alone. Moreover, serplulimab plus chemotherapy improved median OS *vs.* chemotherapy alone by only 4.5 months in the ASTRUM-005 trial (27).

In the present study, the median PFS was 13.6 (95% CI: 11.2–15.6) months and the median OS was 19.5 (95% CI: 14.5–24.5) months, which were higher than those reported in the IMPOWER-133, CASPIAN, ASTRUM-005, and CAPSTONE-1 trials. It has been shown that ICI monotherapy is unsatisfactory as first-line maintenance therapy for ES-SCLC. Results from the CheckMate 451 trial indicated that maintenance therapy with nivolumab plus ipilimumab (median PFS, 1.7 months; median OS, 9.2 months) or nivolumab monotherapy (median PFS, 1.9 months; median OS, 10.4 months) following first-line chemotherapy did not prolong the PFS and OS (28). Gadgeel *et al.* conducted a single-arm phase II study to assess the efficacy of maintenance pembrolizumab in patients with ES-SCLC who had a response or SD after first-line platinum-etoposide chemotherapy, with an ORR of 11.1%, median PFS of 1.4 months, a 6-month PFS of 20.0%, a 12-month PFS of 13.0%, and a median OS of 9.6 months (29). The exploratory analysis in the subset of patients who reached the maintenance phase from the IMPOWER-133 trial demonstrated a median PFS of 2.6 months for maintenance treatment with atezolizumab monotherapy (30). These findings suggest the importance of maintenance therapy in the first-line setting of ES-SCLC and reflect that the survival benefits from first-line maintenance therapy with ICI monotherapy warrant to be further improvement.

Therefore, the excellent survival results in our study were considered to be attributable to the addition of anlotinib in the maintenance therapy. The unsatisfactory efficacy of ICI monotherapy maintenance therapy after first-line chemotherapy plus immunotherapy in ES-SCLC may be associated with the heterogeneity of SCLC as well as primary and secondary immune resistance (31). Since anti-angiogenic therapies can modulate the tumor immunosuppressive microenvironment and eliminate immunosuppression, the combination of anti-angiogenic agents with immunotherapy might overcome primary and secondary immune resistance (32,33). At present, anti-tumor angiogenesis drugs are classified into four main categories: VEGF monoclonal antibodies (e.g., bevacizumab), recombinant human endostatin injection, anti-angiogenesis fusion proteins (e.g., aflibercept), and small-molecule TKIs (e.g., anlotinib, apatinib, sorafenib, etc.). Anlotinib is a multitarget TKI that facilitates tumor vessel normalization by improving the distribution of pericytes/endothelial cells (34) and increases the infiltration of immune cells by downregulating PD-L1 expression on the surface of endothelial cells (35). In addition, anlotinib regulates immune cells to alleviate the immunosuppressive state in the tumor microenvironment (34,36), and modulates cytokine levels to enhance the anti-tumor immune response (35,37,38). A single-arm phase II study revealed the encouraging efficacy of anlotinib plus toripalimab as maintenance treatment after first-line platinum-based chemotherapy in ES-SCLC, with an ORR of 6.7%, a DCR of 80.0%, and a median PFS of 12.5 months (39). The real-world data from this study showed that the addition of anlotinib in the maintenance therapy did not increase the toxicity of ICI monotherapy and had a manageable safety profile. In the present study, grade 3–4 AEs were reported in 58.3% of patients, which was lower than that reported in the IMPOWER-133, CASPIAN, and CAPSTONE-1 trials (66.0–86.0%). Moreover, no life-threatening AEs were observed. All AEs during maintenance therapy were tolerated and were regarded as grade 1–2, with the majority being fatigue, nausea, rash, and hemoptysis. In conclusion, as a multi-target small-molecule anti-tumor angiogenesis drug, anlotinib not only regulates the tumor microenvironment and enhances immune synergism, but also demonstrates good efficacy, mild side effects, and convenient oral administration.

The main limitation of this study was the small sample size. Since there were few anti-PD-1/PD-L1 antibodies available for the first-line treatment of ES-SCLC between 2020 and 2021, and the high economic burden of the study drugs at that time, making only a small percentage of patients in the real-world setting received maintenance therapy with anlotinib and anti-PD-1/PD-L1 antibodies. However, with the approval of more immunologic drugs and the reduction in drug costs in recent years, the treatment regimen is accessible to more patients, allowing us to enlarge our sample size and follow-up more patients. Although the combination of anti-angiogenic agents with immunotherapy has been proven to be a promising therapeutic strategy in the treatment of a variety of solid tumors, there are still many issues that need to be resolved

in clinical practice, such as determining the optimal beneficial populations, optimal dosage, and duration of administration, with the expectation of making the combination regimen more effective and safer, which is also a priority in future research.

Conclusions

The present study demonstrated that anlotinib plus anti-PD-1/PD-L1 antibodies as maintenance therapy after first-line chemotherapy combined with immunotherapy in ES-SCLC could significantly prolong PFS and OS with an acceptable safety profile, which brings new hope for the long-term survival of patients with this disease.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-394/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-394/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-394/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-394/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted following the Declaration of Helsinki (as revised in 2013). Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Army Medical University [No. (B)KY2023090]. Informed consent from patients was exempted from the ethical review due to the retrospective design.

References

1. Li J, Wang Y, Li J, et al. Prognostic Value of Pretreatment D-Dimer Level in Small-Cell Lung Cancer: A Meta-Analysis. Technol Cancer Res Treat 2021;20:1533033821989822.
2. Bernhardt EB, Jalal SI. Small Cell Lung Cancer. Cancer Treat Res 2016;170:301-22.
3. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530-5.
4. Schabath MB, Nguyen A, Wilson P, et al. Temporal trends from 1986 to 2008 in overall survival of small cell lung cancer patients. Lung Cancer 2014;86:14-21.
5. Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. Transl Lung Cancer Res 2018;7:69-79.
6. Horn L, Mansfield AS, Szczęsna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018;379:2220-9.
7. 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;394:1929-39.
8. Qin B, Xin L, Liang C, et al. Efficacy and safety of anti-PD-1 inhibitor versus anti-PD-L1 inhibitor in first-line treatment of extensive-stage small cell lung cancer: a multicenter retrospective study. BMC Cancer 2024;24:100.
9. Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. Nature 2011;473:298-307.
10. Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996;2:1096-103.
11. Schaaf MB, Garg AD, Agostinis P. Defining the role of the tumor vasculature in antitumor immunity and

immunotherapy. Cell Death Dis 2018;9:115.
12. Huang H, Langenkamp E, Georganaki M, et al. VEGF suppresses T-lymphocyte infiltration in the tumor microenvironment through inhibition of NF-κB-induced endothelial activation. FASEB J 2015;29:227-38.
13. Hegde PS, Wallin JJ, Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. Semin Cancer Biol 2018;52:117-24.
14. Hendry SA, Farnsworth RH, Solomon B, et al. The Role of the Tumor Vasculature in the Host Immune Response: Implications for Therapeutic Strategies Targeting the Tumor Microenvironment. Front Immunol 2016;7:621.
15. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity 2014;41:49-61.
16. Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med 2015;212:139-48.
17. Gavalas NG, Tsiatas M, Tsitsilonis O, et al. VEGF directly suppresses activation of T cells from ascites secondary to ovarian cancer via VEGF receptor type 2. Br J Cancer 2012;107:1869-75.
18. Ziogas AC, Gavalas NG, Tsiatas M, et al. VEGF directly suppresses activation of T cells from ovarian cancer patients and healthy individuals via VEGF receptor Type 2. Int J Cancer 2012;130:857-64.
19. Kashyap AS, Schmittnaegel M, Rigamonti N, et al. Optimized antiangiogenic reprogramming of the tumor microenvironment potentiates CD40 immunotherapy. Proc Natl Acad Sci U S A 2020;117:541-51.
20. Qiang H, Chang Q, Xu J, et al. New advances in antiangiogenic combination therapeutic strategies for advanced non-small cell lung cancer. J Cancer Res Clin Oncol 2020;146:631-45.
21. Zhou S, Zhang H. Synergies of Targeting Angiogenesis and Immune Checkpoints in Cancer: From Mechanism to Clinical Applications. Anticancer Agents Med Chem 2020;20:768-76.
22. Kim CG, Jang M, Kim Y, et al. VEGF-A drives TOX-dependent T cell exhaustion in anti-PD-1-resistant microsatellite stable colorectal cancers. Sci Immunol 2019;4:eaay0555.
23. Khalil DN, Smith EL, Brentjens RJ, et al. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 2016;13:273-90.
24. Shi J, Cheng Y, Wang Q, et al. Anlotinib as third- or further-line therapy for short-term relapsed small-cell lung cancer: subgroup analysis of a randomized phase 2 study (ALTER1202). Front Med 2022;16:766-72.
25. He J, Li J, Chen Y, et al. Chinese Society of Clinical Oncology (CSCO) Small-Cell Lung Cancer. Beijing: People's Medical Publishing House; 2020:154.
26. Wang J, Zhou C, Yao W, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2022;23:739-47.
27. Cheng Y, Han L, Wu L, et al. Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients With Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial. JAMA 2022;328:1223-32.
28. Owonikoko TK, Park K, Govindan R, et al. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. J Clin Oncol 2021;39:1349-59.
29. Gadgeel SM, Pennell NA, Fidler MJ, et al. Phase II Study of Maintenance Pembrolizumab in Patients with Extensive-Stage Small Cell Lung Cancer (SCLC). J Thorac Oncol 2018;13:1393-9.
30. Reck M, Mok TSK, Mansfield A, et al. Brief Report: Exploratory Analysis of Maintenance Therapy in Patients With Extensive-Stage SCLC Treated First Line With Atezolizumab Plus Carboplatin and Etoposide. J Thorac Oncol 2022;17:1122-9.
31. Walsh RJ, Soo RA. Resistance to immune checkpoint inhibitors in non-small cell lung cancer: biomarkers and therapeutic strategies. Ther Adv Med Oncol 2020;12:1758835920937902.
32. Bourhis M, Palle J, Galy-Fauroux I, et al. Direct and Indirect Modulation of T Cells by VEGF-A Counteracted by Anti-Angiogenic Treatment. Front Immunol 2021;12:616837.
33. Jain RK. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. Cancer Cell 2014;26:605-22.
34. Su Y, Luo B, Lu Y, et al. Anlotinib Induces a T Cell-Inflamed Tumor Microenvironment by Facilitating Vessel Normalization and Enhances the Efficacy of PD-1 Checkpoint Blockade in Neuroblastoma. Clin Cancer Res 2022;28:793-809.
35. Liu S, Qin T, Liu Z, et al. anlotinib alters tumor immune microenvironment by downregulating PD-L1 expression on vascular endothelial cells. Cell Death Dis 2020;11:309.
36. Li J, Cao P, Chen Y, et al. Anlotinib combined with the PD-L1 blockade exerts the potent anti-tumor immunity in

renal cancer treatment. Exp Cell Res 2022;417:113197.
37. Yuan M, Zhai Y, Men Y, et al. Anlotinib Enhances the Antitumor Activity of High-Dose Irradiation Combined with Anti-PD-L1 by Potentiating the Tumor Immune Microenvironment in Murine Lung Cancer. Oxid Med Cell Longev 2022;2022:5479491.
38. Yuan M, Zhu Z, Mao W, et al. Anlotinib Combined With Anti-PD-1 Antibodies Therapy in Patients With Advanced Refractory Solid Tumors: A Single-Center, Observational, Prospective Study. Front Oncol 2021;11:683502.
39. Lv D, Wu G, Lin L, et al. EP14.01-016 Anlotinib Plus Toripalimab as Maintenance Treatment in Extensive-Stage Small Cell Lung Cancer: a Single-Arm Phase II Study. J Thorac Oncol 2022;17:S533.

Cite this article as: Yang P, Luo H, Zhao L, Xiong F, Tang C. Effectiveness and safety of anlotinib plus anti-programmed cell death 1/ligand 1 (anti-PD-1/PD-L1) antibodies as maintenance therapy after first-line chemotherapy combined with anti-PD-1/PD-L1 antibodies in extensive-stage small cell lung cancer: a real-world study. J Thorac Dis 2024;16(7):4391-4399. doi: 10.21037/jtd-24-394