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ORIGINAL RESEARCH

The Efficacy and Safety of Anlotinib Treatment for Patients with Advanced Non-Small Cell Lung Cancer (NSCLC) Who Achieved Stable Disease (SD) After Two Cycles of First-Line Chemotherapy Combined with Immunotherapy: A Retrospective Cohort Study

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Objective: The maintenance treatment with anlotinib can improve the efficacy in advanced non-small cell lung cancer (NSCLC) patients, but the appropriate patient population are still undefined. This study aimed to evaluate the efficacy and safety of adding anlotinib treatment in advanced NSCLC patients who achieved disease stabilization after two cycles of first-line chemotherapy combined with immunotherapy (CIO).

Materials and Methods: We retrospectively reviewed clinical data of patients with advanced NSCLC who received anlotinib treatment after achieving stable disease (SD) following two cycles of first-line CIO in our hospital. The primary endpoints were progression-free survival (PFS) and overall survival (OS), and the secondary endpoints included objective response rate (ORR), disease control rate (DCR), and Adverse Events (AEs).

Results: A total of 38 patients were included in this study. The median age was 65 years (range, 47–77), with 73.68% male and 26.32% female. The median PFS and OS were 6.5 months and 12.0 months, respectively. The ORR and DCR were 34.21% and 68.42%, respectively. Subgroup analysis results showed that patients who experienced hypertension, proteinuria, and hand-foot syndrome during treatment had better efficacy. Mechanistic analysis further suggested that this regimen may enhance the anti-tumor immunity by depleting Tregs, thereby exerting a synergistic effect. Importantly, the overall AEs of this regimen were manageable, supporting the suitability of this treatment modality.

Conclusion: Adaptive use of Anlotinib could be a safe and effective option in advanced NSCLC patients who achieved SD after two cycles of first-line CIO. This regimen is expected to become an important option for precision and personalized treatment of NSCLC. However, due to the limitations of retrospective nature, its clinical value needs to be further confirmed by prospective studies.

Keywords: anlotinib, immunotherapy, NSCLC, adaptive therapy

Background

Advanced non-small cell lung cancer (NSCLC) remains one of the leading causes of cancer-related mortality worldwide, with a poor prognosis due to late-stage diagnosis and the complexity of tumor biology.[1,2] Traditional treatment

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approaches have included chemotherapy and radiation therapy; however, these modalities often yield limited efficacy while resulted in significant toxicity.[3] The advent of immunotherapy has revolutionized the treatment landscape for NSCLC, particularly with the introduction of immune checkpoint inhibitors (ICIs) that enhance the body's immune response against tumors.[4,5] Despite these advancements, the majority of patients do not achieve complete remission, with many presenting with stable disease (SD) as the best response. This highlights the need for novel therapeutic strategies to optimize treatment outcomes in this challenging population.[6–8]

Anlotinib, a multi-targeted tyrosine kinase inhibitor, has shown promise in treating various malignancies,[9] including NSCLC.[10] It primarily inhibits tumor angiogenesis and progression through targeting vascular endothelial growth factor receptors (VEGFR), platelet-derived growth factor receptors (PDGFR), and fibroblast growth factor receptors (FGFR). Previous evidence has demonstrated that anlotinib had favorable efficacy in NSCLC patients who received otherwise treatment before,[11] thereby, it has been approved as a second-line therapy.[12,13] However, its efficacy and safety profiles in combination treatment of chemotherapy and immunotherapy for NSCLC patients who exhibiting SD has not been extensively investigated.

The rationale for combining anlotinib with chemotherapy and immunotherapy stems from its potential to enhance antitumor activity while mitigating drug resistance associated with tumor growth.[14,15] In this regimen, chemotherapy induces immunogenic cell death, thereby activating T cells, meanwhile, immunotherapy such as ICIs can further amplify this immune response.[16–18] The addition of anlotinib may create a more favorable tumor microenvironment through inhibiting angiogenesis, enhancing the efficacy of immunotherapy.[19–21] Together, this therapeutic modalities could offer a synergistic effect, improving overall survival and progression-free survival in patients who have not achieved optimal responses to standard treatment.[22,23]

Therefore, our study aims to evaluate the efficacy and safety of anlotinib in a cohort of patients with advanced NSCLC who received first-line CIO and exhibited stable disease. We expected that the implication of anlotinib will provide additional therapeutic benefits, enhancing patient outcomes while maintaining an acceptable safety profile.[23] Ultimately, this strategy may help overcome the challenge of poor responsiveness to early therapy and suboptimal long-term efficacy in this population. Hopefully, our findings may contribute to establishing an evidence-based framework for integrating anlotinib into the treatment paradigm of advanced NSCLC, particularly for those with stable disease, enhancing the overall patient care and outcomes in this disease setting.

Materials and Methods

This retrospective study was conducted at Hubei Cancer Hospital. We reviewed the medical records of NSCLC patients treated between January 2021 to December 2023 who received first-line chemotherapy combined with immunotherapy, followed by anlotinib in cases where stable disease (SD) was achieved. Due to the retrospective design of the study, the requirement for informed consent was waived.

Patient Selection Criteria

Patients were eligible for inclusion when they met the following criteria: (1) confirmed diagnosis of advanced NSCLC, (2) received two cycles of first-line chemotherapy in combination with an immune checkpoint inhibitor (eg, pembrolizumab, nivolumab, or atezolizumab), (3) achieved stable disease after initial treatment, as assessed by RECIST v1.1 criteria, and (4) subsequently initiated anlotinib therapy.

Exclusion criteria include: (1) prior treated with targeted therapy or investigational agents, (2) had serious concurrent medical conditions, and (3) loss to follow-up.

Lymph Cell Subpopulation Analysis by FCAM

Blood samples were collected in ethylenediamine tetraacetic acid (EDTA) tubes from advanced NSCLC patients before and after treatment. Samples were processed within 6 hours of collection. CD3+/CD4+/CD8+ T-cell, CD19+ B-cell, and CD16+CD56+ natural killer (NK) cell counts (cells/μL) were quantified using multicolor flow cytometry with human monoclonal anti-CD3-fluorescein isothiocyanate (FITC), anti-CD4-phycoerythrin (PE), anti-CD8-allophycocyanin (APC), anti-CD19-PE, anti-CD16-APC, and anti-CD56-PE antibodies [BD Multitest; Becton, Dickinson, and Co.

(BD) Biosciences, Franklin Lakes, NJ, USA] following the manufacturer's instructions. The cells were analyzed using a BD FACS Canto II flow cytometry system (BD Biosciences).

Treatment Protocol

NSCLC patients with negative driver genes mutation who achieved SD after two cycles of first-line CIO were administered additional Anlotinib therapy while continuing the CIO treatment for two more cycles, followed by maintenance treatment with Anlotinib in combination with single-agent chemotherapy and immunotherapy. Anlotinib was administrated orally at a dose of 12 mg once daily for 2 weeks, followed by a 1-week break. The dose could be reduced to 10 mg or 8 mg in the event of severe AEs. Treatment was permanently discontinued if the 8 mg dose was still intolerable. Anlotinib was continued until disease progression or the occurrence of intolerable AEs.

Assessment of Efficacy and Safety

Efficacy endpoints included ORR, DCR, PFS and OS. ORR was defined as the proportion of patients achieving complete or partial response. DCR was defined as the proportion of patients with complete response, partial response, or stable disease. PFS was defined as the time from the initiation of anlotinib treatment until disease progression or death from any cause. OS was measured from the start of anlotinib treatment until death from any cause.

Safety was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. All AEs were recorded and graded based on their severity, with particular attention to hypertension, fatigue, gastrointestinal disturbances, and any serious adverse events leading to treatment discontinuation or dose modification.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and treatment outcomes. Survival analyses were performed using the Kaplan-Meier method, and differences in survival curves were assessed with the Log rank test. Statistical significance was defined as a two-sided p-value of <0.05. All analyses were conducted using SPSS 13.0.

Results

Patients' Characters

A total of 38 advanced NSCLC patients who received first-line CIO and subsequently underwent anlotinib treatment after achieving stable disease (SD) were retrospectively reviewed. The medium age was 65 (range, 47–77) years, with 73.68% of patients being male and 26.32% female. 78.95% patients had a smoking history. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 73.68% of patients or 1 in 26.32%. Patients were stratified based on metastatic sites, with brain, bone, and liver metastases were observed in 28.95%, 34.21%, and 23.68% of patients, respectively. Besides, according to PD-L1 expression, patients were categorized into three groups: PD-L1 < 1% (28.95%), 1% ≤PD-L1 < 49% (34.21%), and PD-L1 ≥ 50% (23.68%). Patients were also grouped based on clinical stage. The proportions of patients in stages IVA, IVB, and IVC were 18.42%, 28.95%, and 52.63%, respectively (See Table 1).

Efficacy Outcomes

All 38 patients were eligible for treatment response evaluations. The median PFS and OS, calculated from the initiation of anlotinib treatment, were 6.5 months and 12 months, respectively (See Table 2). The ORR and DCR were 34.21% and 68.42%, respectively.

Further analysis showed no statistically significant difference in mPFS and mOS between PD-L1 (+) and PD-L1 (-) patients (PD-L1 (+) vs PD-L1 (-), mPFS, 6.0 months vs 7.0 months, P=0.4978, HR=0.8571, 95% CI: 0.3282–1.386; mOS, 11.0 months vs 12.5 months, with P=0.0565, HR=0.8800, 95% CI: 0.3510–1.409. These finding suggest that PD-L1 expression level has no obvious impact on benefit of this regimen. Additionally, subgroup analysis revealed that patients who experienced AEs, such as hypertension, proteinuria, and hand-foot syndrome, had improved efficacy compared to those who did not (with sAE vs without sAEs, mPFS 7.0 months vs 6.0 months, P=0.0004, HR=1.167, 95% CI: 0.6449–1.688; mOS 13.0 months vs 11.0 months, P=0.0014, HR=1.182, 95% CI: 0.6600–1.704) (See Figure 1).

Table 1 Baseline Clinical Characteristics of the Study Cohort

Characteristics	No. of Patients (%)
Age	
Years	65
Range	47-77
Gender	
Male	28(73.68%)
Female	10(26.32%)
Smoking history	
Never smoker	8(21.05%)
Former smoker	30(78.95%)
Histology	
Adenocarcinoma	23(60.53%)
Squamous carcinoma	15(39.47%)
ECOG score	
0	28(73.68%)
1	10(26.32%)
PD-L1 expression level	
<1%	20(52.63%)
1-49%	16(42.11%)
≥50%	2(5.26%)
Previous Radiotherapy	
Yes	6(15.79%)
No	32(84.21%)
Brain metastasis	
Yes	11(28.95%)
No	27(71.05%)
Bone metastasis	
Yes	13(34.21%)
No	25(65.79%)
Liver metastasis	
Yes	9(23.68%)
No	29(76.32%)
Stage	
IVA	7(18.42%)
IVB	11(28.95%)
IVC	20(52.63%)

Table 2 The Clinical Activities of Anlotinib in Adaptive Therapy for Patients with Advanced NSCLC Who Achieved Stable Disease (SD) After Two Cycles of First-Line Chemotherapy Combined with Immunotherapy

	Patient No.	Ratio
Complete response	0	0
Partial response	13	34.21%(13/38)
Stable response	13	34.21%(13/38)
Progressive disease	12	31.58%(12/38)
Objective response		34.21%
Median PFS		6.5m
Disease control Rate		68.42%
Median OS		12.0m

These results indicate that the occurrence of specific AEs may serve as a potential biomarker for identifying patients more likely benefit from this regimen.

Mechanism Study

We first examined changes of immune cells in the peripheral blood before and after treatment. Notably, Tregs were significantly elevated following two cycles of CIO, suggesting the establishment of an immunosuppression microenvironment. Interestingly, the Tregs markedly reduced after completing 6 weeks of combined therapy. Moreover, patients who experienced Treg reduction at the end of treatment had higher overall response rates (ORR) and disease control rates (DCR) compared to those did not. Also, patients with Treg depletion demonstrate prolonged median mPFS and mOS compared to their counterparts (Treg depletion vs no Treg depletion: mPFS 7.0 months vs 5.0 months, P<0.0001, HR=1.400, 95% CI: 0.8782–1.922; mOS 13.0 months vs 10.0 months, P<0.0001, HR=1.300, 95% CI: 0.7782–1.822) (See Figure 2). These results indicated that this regimen may induce Tregs depletion, thereby ameliorate the immunosuppressive status, ultimately exhibited a synergistic anti-tumor effect. Therefore, the reduction in Treg levels could serve as a molecular biomarker for efficacy prediction.

Safety Profile

The treatment was generally well-tolerated, with most AEs being manageable. Overall, 47.36% of patients experienced at least one grade 3 or higher AE. The most common serious AEs included bone marrow suppression (leukopenia, neutropenia, accounting for 10.53%), antitumor angiogenesis drug-related adverse AEs (hypertension, hand-foot syndrome, proteinuria, accounting for 15.79%), and immune-related AEs (rash, hepatitis, accounting for 7.89%). No grade 5 AE or treatment-related deaths occurred during the study period. Only three patients (7.89%) discontinued anlotinib due to AEs, primarily grade 3 hypertension (2.63%), hand-foot syndrome (2.63%), and proteinuria (2.63%). Other notable AEs included neutropenia (5.26%), rash (5.26%), and leukopenia (5.26%), which were resolved with dose adjustment or supportive care (see Table 3).

Discussion

The treatment landscape for advanced non-small cell lung cancer (NSCLC) has undergone a transformative change over the past decade, particularly driven by the advent of immunotherapy and targeted agents.[2,3] In this retrospective study, we evaluated the efficacy and safety of anlotinib in patients with advanced NSCLC who achieved stable disease (SD) following first-line chemotherapy combined with immunotherapy (CIO).[23] Our findings provide critical insights into the potential role of anlotinib as an adaptive therapy in this patient population.[24,25]

The primary objective of our analysis was to assess the outcomes of those patients. Firstly, we observed a median PFS of 6.5 months and an OS of 12 months, both notably longer compared with outcomes in patients received CIO alone.[26,27]

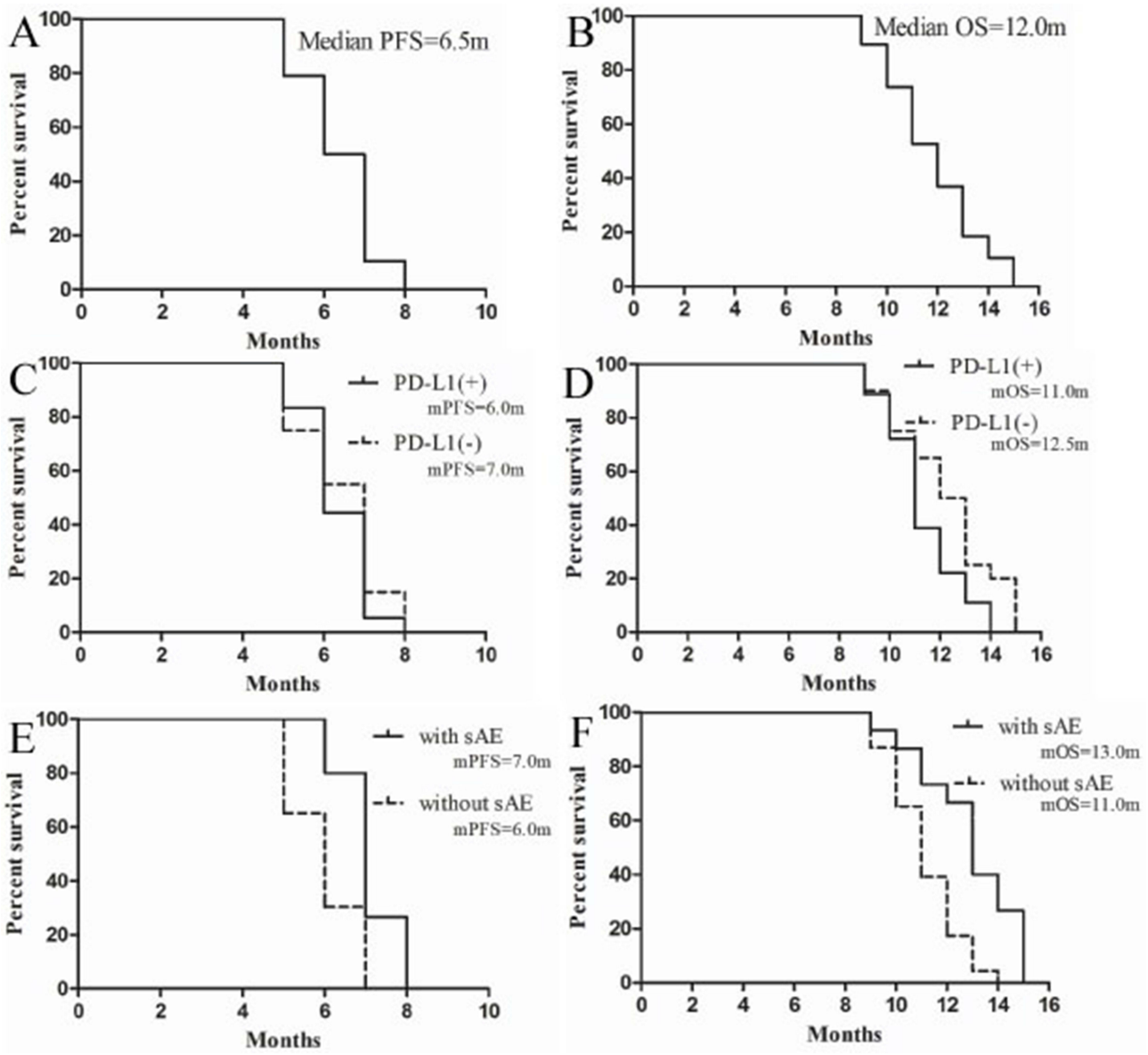

Figure 1 The median progression-free survival (PFS) and overall survival (OS) of patients with advanced NSCLC who achieved stable disease (SD) after two cycles of first-line chemotherapy combined with immunotherapy and received adaptive therapy with anlotinib. (**A** and **B**) represent the median PFS and OS for the general population, respectively; (**C** and **D**) show comparisons of PFS and OS between patients with PD-L1 (+) and patients with PD-L1 (-) (PD-L1 (+) vs PD-L1 (-). (**E** and **F**) show comparisons of PFS and OS between patients with and without specific adverse events (sAEs) during the entire treatment (with sAE vs without sAE). PD-L1 (+) is defined as a PD-L1 expression level ≥1%, and PD-L1 (-) is defined as a PD-L1 expression level <1%. mPFS, median progression-free survival; mOS, median overall survival; sAE specifically refers to any adverse event, including hypertension, proteinuria, and hand-foot syndrome.

Furthermore, the ORR of 34.21%, along with the significant benefit observed during anlotinib treatment,[10] underscores its importance as sequential treatment for managing advanced NSCLC.[28]

In terms of safety, anlotinib was generally well-tolerated. AEs were reported in 75% of patients, with the most frequently AEs being hypertension (31.58%), hand-foot syndrome (28.95%), and proteinuria (26.32%), consistent with its known safety profiles.[29] Most AEs were manageable through dose modifications or symptomatic treatments, and only 10% of patients discontinued therapy due to severe toxicities.[30] Collectively, these data indicated that anlotinib can be incorporated into clinical practice without substantially compromising patients' quality of life.[31]

To our knowledge, this is the first time to investigate on the suitability of anlotinib in treating advanced NSCLC patients who achieved SD after two cycles of CIO.[23,32] Importantly, our cohort included patients with traditionally unfavorable prognostic factors such as liver and brain metastases[33,34] and low PD-L1 expression, broadening clinical

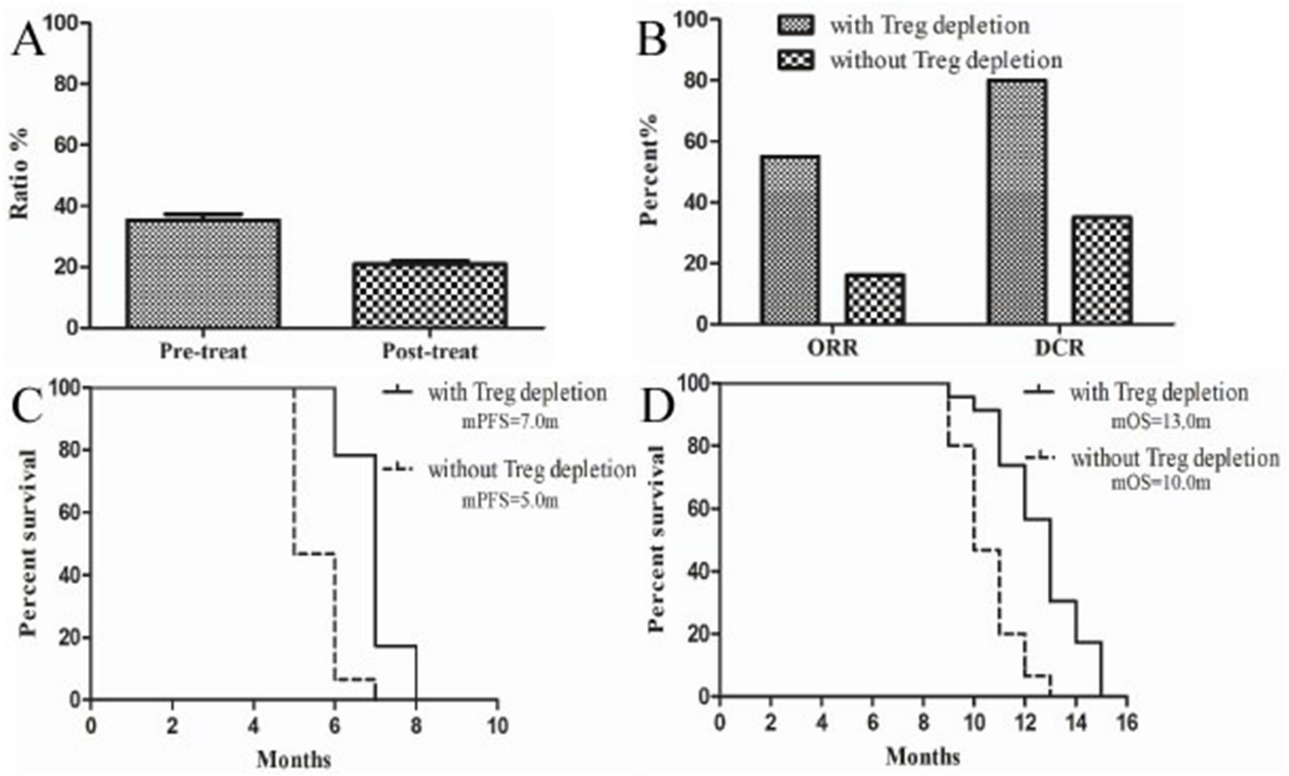

Figure 2 The association between the efficacy of adaptive therapy with anlotinib in patients with advanced NSCLC who achieved stable disease (SD) after two cycles of first-line chemotherapy combined with immunotherapy and the changes in the proportion of Tregs in peripheral blood before and after treatment. (**A**) shows the changes in Treg proportions before and after treatment; (**B**) represents the ORR and DCR in different populations after treatment based on Treg depletion status (with Treg depletion vs without Treg depletion); (**C** and **D**) illustrate the PFS and OS comparisons among different populations after treatment based on Treg depletion status (with Treg depletion vs without Treg depletion).

application of this approach.[11] Furthermore, patients who developed hypertension, proteinuria, and hand-foot syndrome exhibited better efficacy, suggesting that these AEs could serve as potential predictive markers for treatment benefit.[30,35] These findings warrant further investigation to support precision and individualized treatment of advanced NSCLC.[36]

Mechanistic study revealed that patients with SD after two cycles of CIO generally present an immunosuppressive microenvironment. This may explain the poor efficacy observed in this subgroup, while also providing a rational for the early intervention of other treatment modalities, such as anti-tumor angiogenesis small molecule inhibitors like anlotinib.[23,25] Interestingly, immunosuppressive status appeared to be reversed after completion of 6 cycles of treatment, likely through Treg depletion. These results suggest that this regimen may exert synergistic anti-tumor effects by alleviating immune suppression and reactivating antitumor immunity.[21] Consistently, our data support that anti- angiogenic therapy not only improves the unfavorable immune microenvironment but also influence the proportion of peripheral blood Treg cells.[37,38] Nevertheless, the precise mechanism by which Tregs are regulated remain unclear and will be an important focus in our future work.[16]

Despite these promising findings,[22] several limitations must be acknowledged. As a retrospective study, it is subject to inherent biases, including selection bias and confounding factors that could influence treatment outcomes.[39] Additionally, the small sample size, limits the generalizability of our findings.[33] Future prospective studies with larger cohorts and longer follow-up periods are warranted to validate the results and elucidate the role of anlotinib in the treatment of advanced NSCLC.[40] Moreover, the potential synergistic effects of combining anlotinib with other targeted agents or immunotherapies can be explored, particularly in biomarker-driven populations.[41] The ongoing development of novel agents and combination therapies may provide additional options for patients with advanced NSCLC, necessitating continuous evaluation of promising treatment strategies.[42–44]

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Table 3 The AEs of Anlotinib in Adaptive Therapy for Patients with Advanced NSCLC Who Achieved Stable Disease (SD) After Two Cycles of First-Line Chemotherapy Combined with Immunotherapy

Adverse Event	Adaptive Treatment of Anlotinib [n(%)]	
	Any Grade	Grade 3 or 4
Hematological		
Leukopenia	13(34.21%)	2(5.26%)
Neutropenia	14(36.84%)	2(5.26%)
Thrombocytopenia	11(28.95%)	1(2.63%)
Anemia	10(26.32%)	0%
Nonhematologic		
Decreased appetite	17(44.74%)	0%
Fatigue	13(34.21%)	0%
Hypertension	12(31.58%)	2(5.26%)
Hand-foot syndrome	11(28.95%)	2(5.26%)
Proteinuria	10(26.32%)	2(5.26%)
Peripheral neuropathy	8(21.05%)	1(2.63%)
Elevated transaminase	7(18.42%)	1(2.63%)
Oral ulcer	6(15.79%)	0%
Stomatitis	5(13.16%)	0%
Abdominal pain	4(10.53%)	0%
Diarrhea	4(10.53%)	0%
Hyperbilirubinemia	3(7.89%)	0%
Elevated LDH	2(5.26%)	0%
ALP increased	2(5.26%)	0%
Elevated GGT	2(5.26%)	0%
Hypoproteinemia	2(5.26%)	0%
Dysphagia	2(5.26%)	0%
Dysphonia	2(5.26%)	0%
Bleeding	0%	0%
Immunological		
Hypothyroidism	13(34.21%)	0%
Hyperthyroidism	11(28.95%)	0%
Rash	10(26.32%)	2(5.26%)
Hepatitis	7(18.42%)	1(2.63%)
Itching	6(15.79%)	1(2.63%)
Pneumonia	4(10.53%)	1(2.63%)
Infusion reaction	3(7.89%)	0%
Nephritis	2(5.26%)	0%

In conclusion, our study highlights the potential of anlotinib as an effective and safe adaptive therapy in patients with advanced NSCLC who achieve stable disease after first-line chemotherapy and immunotherapy. The mechanism of action is likely due to the depletion of Tregs, which further activates immunity to exert a synergistic anti-tumor effect.[45] Owing to its favorable efficacy and low toxicity, this regimen not only provides a basis for precision and personalized treatment of NSCLC but may also represent an important treatment option for this group of patients.[46] Nevertheless, the current study inevitably has some limitations, such as a small sample size, a retrospective design, data primarily from a single center, lack of predictive efficacy biomarkers, unclear resistance mechanisms, and unknown long-term toxic side effects. It is believed that with the continuous progress of research, the value of anlotinib in NSCLC adaptive treatment will be

further explored,[47,48] and more patients will benefit from the treatment, making NSCLC treatment more precise and personalized.[49,50]

Data Sharing Statement

The data produced in this study are accessible upon reasonable request from the corresponding author.

Ethics Approval and Patient Data Confidentiality

This study is a retrospective analysis that received approval from the Ethics Committee of Hubei Cancer Hospital Affiliated with Tongji Medical College (Wuhan, China) (Approval No.: [Approval No. HBCHEC2021107]). Given the retrospective nature of the research, and the fact that all data were anonymized prior to analysis, with no additional risk to patients, the Board waived the requirement for individual informed consent. We are committed to ensuring the privacy of all patients. During data extraction and analysis, all personally identifiable information (such as names, hospital ID numbers, etc.) was removed and replaced with unique anonymized study identifiers. The manuscript will not include any information that could potentially reveal the identity of any patient.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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