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Original Article

Combination of anlotinib and second-line chemotherapy as surrogate to reduce immunosuppression in patients with advanced non-small cell lung cancer

Zhi Lou[1], Xin Wang[2], Chenxi Hu[3], Weixuan Liu[4], Yajun Ji[5]

ABSTRACT

Objective: To study the clinical effects of anlotinib combined with second-line chemotherapy (SLC) on immunosuppression in patients with advanced non-small cell lung cancer (NSCLC).

Methods: In this retrospective study, the medical records of 106 patients with advanced NSCLC admitted to the Lianyungang First People's Hospital from November 2020 to March 2022 were retrospectively analyzed. Amongst 106 patients, 53 patients received second-line single-agent chemotherapy regimens (SLC group), and 53 patients received anlotinib combined with SLC (ASLC group). Prognosis, levels of immune cells and inflammatory cytokine, and adverse reactions were analyzed.

Results: Clinical efficacy of the ASLC group was significantly higher than the SLC group ($p \leq 0.05$). After treatment, patients in the ASLC group exhibited significantly higher levels of CD4+/CD8+ and CD4+ compared to those in the SLC group ($p < 0.05$), while the difference in CD8+ level between the two groups was not statistically significant ($p > 0.05$). After treatment, levels of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), interleukin-8 (IL-8), interleukin-6 (IL-6) in the ASLC group were lower compared to the SLC group ($p \leq 0.05$).

Conclusion: In patients with advanced NSCLC, anlotinib combined with SLC is associated with higher levels of immune cells and reduced inflammatory factors. This treatment regimen, thus, can reduce immunosuppression and improve the prognosis of NSCLC patients.

KEYWORDS: Anlotinib, Non-small cell lung cancer, Immunosuppression, Immune cells, Inflammatory cytokines, Second-line chemotherapy.

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INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for about 80.0% of all lung cancer cases.[1] Due to the complicated pathogenesis of NSCLC and the lack of early symptoms, most NSCLC patients are diagnosed with stage IIB–IV, past the optimal timing of surgical resection.[2,3] Due to the complex pathogenesis of non-small cell lung cancer, high intra-tumor heterogeneity, atypical early symptoms and lack of effective early screening methods, most patients with lung cancer are in local advanced stage or have distant metastases and cannot undergo radical surgical resection.

Platinum-based chemotherapy (PBC), which can decelerate tumor growth and impede disease progression, is currently the preferred treatment for NSCLC.[4,5] However, studies have shown that while PBC can extend the survival duration and enhance the life quality of NSCLC patients, it does not have a curative effect.[6,7] Some patients also develop post-chemotherapy drug tolerance that leads to cancer recurrence.[7] At

present, no agreed standard approach exists for retreatment after failure of first-line chemotherapy (FLC), and patient survival after second-line therapy (SLT) remains extremely low.[8] Therefore, it is crucial to explore treatment options for patients with advanced NSCLC who have failed first-line treatment.

Anlotinib is a new oral multi-target tyrosine kinase inhibitor (TKI) that can effectively inhibit vascular endothelial growth factor receptors (VEGFR), and is used for the treatment of advanced NSCLC.[9] Anti-angiogenic drugs can normalize blood vessels, improve the tumor microenvironment, and promote immune cells and lymphocytes to enter tumor tissues more easily. Moreover, VEGFR-TKIs combined with chemotherapy can promote the transport of chemotherapy drugs into tumor tissues, thus improving the effect of chemotherapy. VEGFR-TKIs combined with chemotherapy have been widely used clinically in the treatment of patients with advanced NSCLC. However, there are few studies on anlotinib combined with chemotherapy as a second-line treatment for patients with NSCLC. Therefore, this study aimed to explore the clinical effects of anlotinib combined with second-line chemotherapy (SLC) on the levels of inflammatory factors and immune cells in patients with advanced NSCLC.

METHODS

In this retrospective study, the medical records of 106 patients (59 males and 47 females) with advanced NSCLC, who were treated in Lianyungang First People's Hospital from November 2020 to March 2022 were analyzed.

Ethical Approval: The ethical approval was taken from the Ethics Committee of Lianyungang First People's Hospital (No. LW-20240123001-01). Patient consent was waived due to the retrospective nature of the study.

Average age of the patients was (59.23±6.42) years old. Patients were divided into two groups: SLC group (n=53) and ASLC group (n=53). The SLC group received standard SLC, and the ASLC group received anlotinib combined with SLC. The diagnostic criteria of NSCLC were based on the lung mass present on pulmonary computer tomography (CT) scan and confirmed by cytology or pathological analysis.

Inclusion criteria:

- Age 18-75 years old.
- NSCLC confirmed by pathology or cytology.[10]
- Patients with stage IIB IIIb-IV.
- Foci detectable via imaging.
- Acquired resistance to drug or recurrence subsequent to FLC.
- Disease progression after first-line TKI treatment, presence of anaplastic large-cell lymphoma kinase, ROS1 mutations, or epidermal growth factor receptor, no previous history of systemic chemotherapy, negative T790M by secondary gene test.
- Eastern Cooperative Oncology Group (ECOG) score of 0-2 points.
- No allergic reactions to the medications used in the study.
- Estimated survival time > six months.

Exclusion criteria:

- Patients with poor blood pressure control.
- Patients who have had a thrombotic event within the past six months.
- Complicated with other malignant tumors or had distant metastases.
- History of anti-vascular targeted drug therapy.
- Patients complicated with autoimmune system diseases.

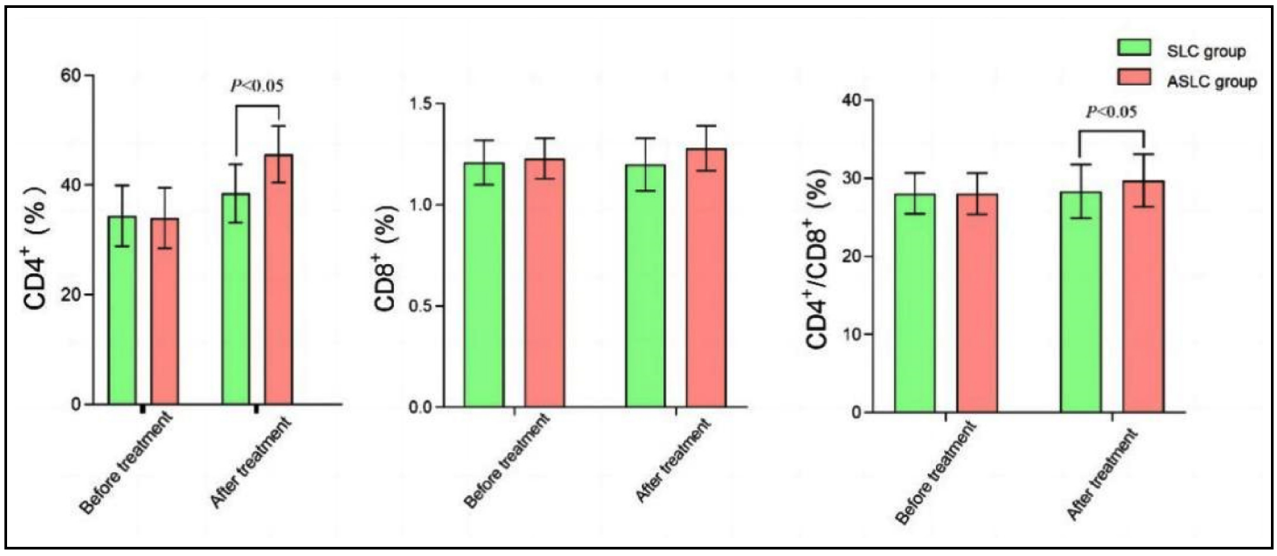

Fig.1: Comparison of immune cell between the groups.

- Insufficiency or severe dysfunction of kidney, liver, heart and other important organs.
- Intolerance for allergic constitution or chemotherapy.
- Impaired cognition or abnormal behavior.

ASLC group (anlotinib combined with chemotherapy regimen): Patients were given anlotinib capsules (Chiatai Tianqing Pharmaceutical Group, National Approval No. H20180004, specification: 12mg/ granule) orally prior breakfast. The starting dosage was 12mg administered once daily, and was discontinued a week after continuous application of two weeks. In case of intolerance to the 12 mg dosage, the dosage was adjusted to 8 mg or 10 mg daily, and treatment continued until the patient reached complete intolerance or disease progression. Throughout this period, patients received monotherapy (pemetrexed 500 mg/m^2 in 1st day or docetaxel 75 mg/m^2 in 1st day). The treatment cycle lasted for 21 days.

SLC group (standard second-line chemotherapy (SLC): Patients were intravenously infused pemetrexed 500 mg/m^2 (Jiangsu Hengrui Pharmaceuticals Co, Ltd., National Approval No.H20133216, specification: 0.2g) within 0 minute to 40 minutes. The medication was administered once every three weeks, constituting one cycle, and four treatment cycles were administered.

During the treatment, patients' conditions and adverse reactions were closely monitored. Symptomatic treatment was provided for patients experiencing Grade 1-2 adverse reactions. In case of Grade 3-4 adverse drug reactions, the drug dosage was decreased or stopped. The duration of the treatment in both groups was 12 weeks.

Observation indicators: Venous blood after six months of therapy were analyzed. A volume of 5mL of venous blood was collected from the patients while fasting, and the serum sample was stored at - 80℃ for subsequent analysis of following:

(1) Levels of immune cells: CD4$^+$, CD8$^+$ and CD4$^+$/ CD8$^+$ were assessed using flow cytometry. Following the placement of serum samples at room temperature, an equivalent volume of 2% paraformaldehyde was added and incubated for 15 minutes. Platelets were then suspended in PBS-EDTA buffer, washed twice, and 100 µl of platelet suspension was analyzed by flow cytometry. The levels of immune cells were evaluated using Cellquest software.

(2) Levels of inflammatory factor: Serum levels of TNF-α, IL-10, IL-8, and IL-6 were assessed using enzyme-linked immunosorbent assay (ELISA), with the kits from Wuhan Boster Biological Technology, LTD. The absorbance was measured using ELISA reader (Agilent, USA) at the wavelength of 450 nm.

The adverse events were assessed based on the Common Terminology Criteria for Adverse Events v4.0 (CT-CAE 4.0), including leukopenia, nausea and vomiting, alopecia, and liver function damage. The adverse events were categorized into grades 0–IV, with higher grades indicating more serious adverse reactions.[11]

The clinical effect was assessed after four cycles of chemotherapy, and was categorized into four levels based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).[12]

Complete remission (CR): complete disappearance of tumor, and the remission lasts ≥ one month;

Partial relief (PR): The product of the tumor's maximum diameter and maximum vertical diameter decreased by over 50%, and the remission lasted ≥ four weeks;

Stable disease (SD): The total length of the lesions increased without reaching PD or decreased without reaching PR;

Progression of disease (PD): The product of tumor's maximum diameter and maximum vertical diameter, increased by over 25%, or appearance of new lesion.

Finally, response rate was calculated as below:

Response rate = cases of (CR+PR)/total cases ×100%

Statistical Analysis: SPSS 23.0 was used for analysis. Normally distributed measurement data were presented as mean ± standard deviation ($\bar{\chi}\pm S$), and were compared using *t* test. Counting data were presented as number and percentage (n, %), and were

Table-I: General characteristics of the two groups.

Characteristics		*SLC group (n=53) [n(%)]*	*ASLC group (n=53) [n(%)]*	χ^2/t	*p-value*
Gender	Male	30 (56.60)	29 (54.72)	0.790[a]	0.433
	Female	23 (43.40)	24 (45.28)		
Age (years)		59.54±6.22	59.12±6.63	0.647[b]	0.511
Lesion diameter (cm)		3.85±0.27	3.83±0.29	0.282[b]	0.770
BMI (kg/m^2)		22.84±1.36	22.37±1.64	0.478[b]	0.672
Clinical classification	Class III	16 (30.19)	18 (33.96)	0.265[a]	0.631
	Class IV	37 (69.81)	35 (66.04)		

[a], indicates statistical value of Chi-square test; [b], indicates statistical value of t test.

Table-II: Comparison of clinical effects between the groups (%).

Group	*CR [n(%)]*	*PR [n(%)]*	*SD [n(%)]*	*PD [n(%)]*	*Objective response rate [n(%)]*
SLC group (n=53)	5 (14.28)	18 (33.96)	21 (39.62)	9 (16.98)	23 (43.39)
ASLC group (n=53)	11 (20.75)	23 (43.39)	16 (30.19)	3 (5.67)	34 (64.15)
χ^2	-	-	-	-	11.132
p-value	-	-	-	-	<0.001

compared using Chi-square test. A p-value ≤0.05 was considered statistically significant.

RESULTS

A total of 106 (N) patients were included in this study. There were 53 cases in the SLC group and 53 cases in the ASLC group, with no statistically significant difference in general data between the groups (p>0.05) (Table-I). The clinical efficacy of the ASLC group was significantly higher than that of the SLC group (p≤0.05) (Table-II).

Before treatment, no significant difference was found in the levels of immune cells between the groups (p>0.05). After treatment, patients in the ASLC group exhibited significantly higher levels of CD4+/ CD8+ and CD4+ compared to those in the SLC group (p≤0.05), while the difference in $CD8^+$ level between the two groups was not statistically significant (p≥0.05) (Fig.1).

Before treatment, no significant difference was found in the level of immune cells between the two groups (p>0.05). After treatment, levels of TNF-α, IL-10, IL-8, and IL-6 in patients of the ASLC group were lower than those of the SLC group (p≤0.05) Fig.2 No significant difference was found in the incidences of alopecia, liver damage, nausea and vomiting, and leukopenia between the groups (p>0.05) Table-III.

DISCUSSION

The results of this study showed that the combination of anlotinib and SLC can improve the levels of immune cells and inflammatory factors in patients with advanced NSCLC, and improve their objective response rate. Our results are consistent with previous studies.[13-15] Wang et al, have shown that the combination of anlotinib and chemotherapy may be effective and well-tolerated for advanced NSCLC patients who have failed first-line or SLT.[13] The study by He et al, also suggests that the combination of anlotinib and pemetrexed as maintenance therapy may be the best choice for treating patients with advanced wild-type EGFR/ALK non-squamous cell carcinoma and NSCLC.[14] In addition, Li et al, showed good efficacy and tolerable safety of anlotinib combined with anti PD-1 inhibitors in second-line or late-stage treatment of patients with advanced solid tumors.[15]

Numerous studies have showed that the occurrence and development of NSCLC is a multi-factor process, and angiogenesis plays a crucial role is the pathophysiology of invasion and metastasis of this type of cancer.[16,17] Therefore, inhibition of angiogenesis remains the main strategy of LC treatment.[18] Anlotinib, a multi-target TKI, halts tumor progression by inhibiting cell migration and capillary formation in endothelial cells.[19] Anlotinib has been demonstrated to be effective in advanced NSCC, and has been approved as a third-line therapy for patients with advanced disease.[20] However, data of anlotinib as the SLT of advanced NSCC are still scarce.[19,20]

Our findings showed a significant superior clinical effect in the ASLC group compared to the SLC group, which is consistent with Wang et al.[13] In addition, no statistical difference was found in the incidence of adverse reactions between the groups. Moreover, the current study revealed that the adverse reactions

Table-III: Comparison of adverse reaction between the groups.

Adverse reactions	*SLC group (n=53) [n(%)]*	*ASLC group (n=53) [n(%)]*	χ^2	*p-value*
Nausea	9 (16.98)	10 (18.86)	0.543	0.745
Liver damage	3 (5.67)	4 (7.54)	0.000	1.000
Alopecia	7 (13.20)	5 (9.43)	0.752	0.671
Leukopenia	4 (7.54)	3 (5.67)	0.421	0.802
Total rate for adverse reactions	23 (43.39)	22 (41.51)	0.015	0.985

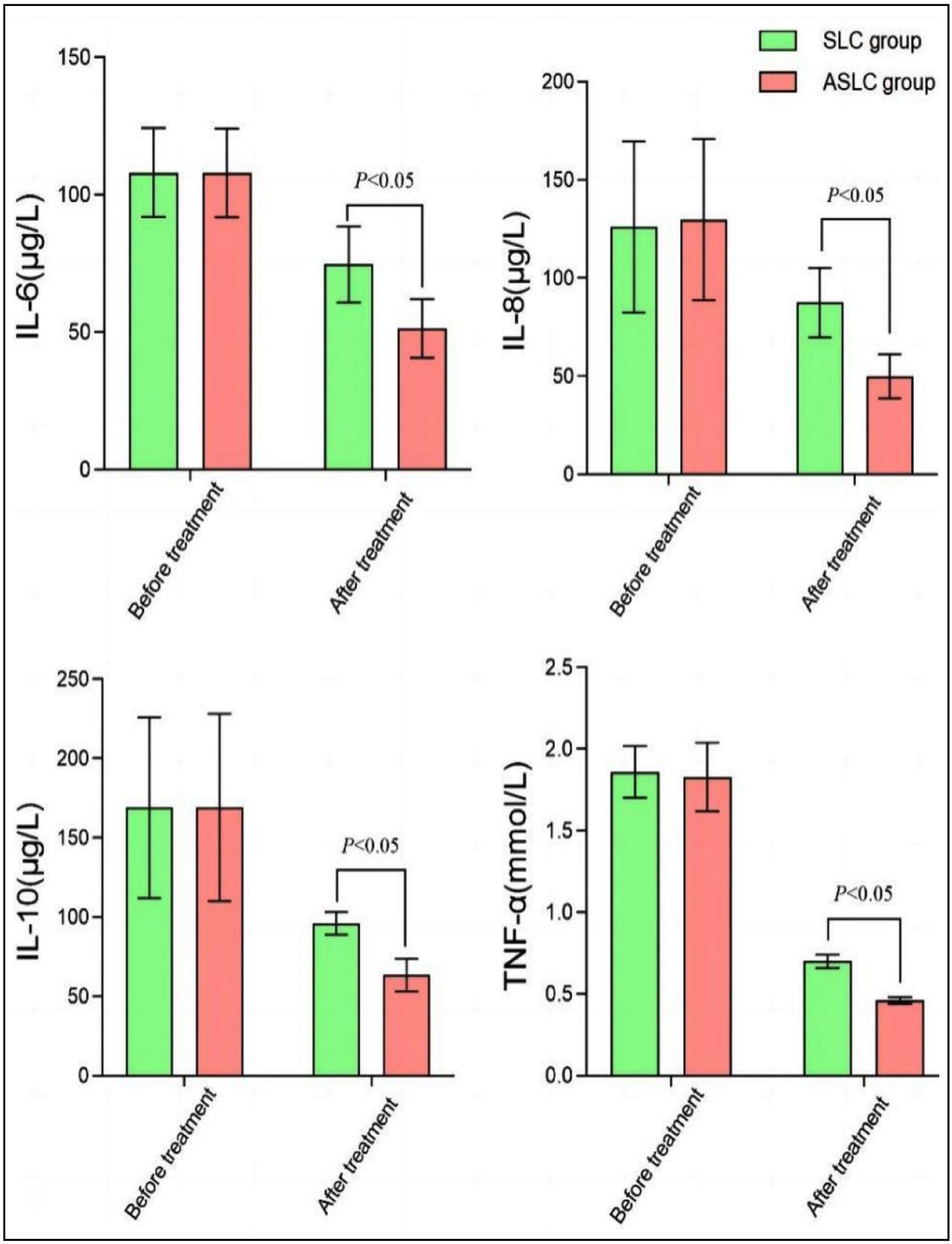

Fig.2: Comparison of inflammatory factors between two groups.

of anlotinib combined with SLC were mainly at grade 1-2, with a low incidence of grade III, and no occurrences of grade IV or severe mortality risk. Most symptoms could be relieved or alleviated after reducing the dosage of the drug or by withdrawal, under close monitoring and symptomatic treatment. Our results showed that the combined treatment can improve the clinical effect with safe profile. As shown by recent studies, anti-angiogenic medications can inhibit tumor angiogenesis, promote normalization of tumor blood vessels, enhance the delivery of drugs to tumor tissues, and counteract drug resistance.[21,22]

Chemotherapy generally has a damaging effect on the functions of multiple tissues and organs, mainly in the form of immunosuppression, as well as subsequent adverse reactions such as bone marrow suppression and infections.[23] Studies have also showed that the levels of $CD4^+/CD8^+$ and $CD4^+$ in patients with LC decrease after chemotherapy.[24] However, the present study showed that patients in the ASLC group exhibited significantly higher levels of CD4+/CD8+ and CD4+ compared to those in the SLC group after treatment. Our findings are basically consistent with Chen et al.[25] Therefore, it is speculated that anlotinib combined with SLC can preserve the immune function of patients with NSCLC to some extent.

Our results also showed that after the treatment, ASLC group showed lower levels of TNF-α, IL-10, IL-8, and IL-6 compared to the SLC group, which is consistent with Zou et al.[26] IL-6 was shown to act directly on LC cells or facilitate the proliferation of tumor cells indirectly. IL-8 promotes tissue angiogenesis and increases the chances of tumor metastasis.[27,28] At the same time, IL-10 can suppress the proliferation and differentiation of T cells and down-regulate the body's anti-tumor response.[27-29]because of their low selectivity, most small molecule inhibitors of VEGFR2 tyrosine kinase show unexpected adverse effects and limited anticancer efficacy. In the present study, we detailed the pharmacological properties of anlotinib, a highly potent and selective VEGFR2 inhibitor, in preclinical models. Anlotinib occupied the ATP-binding pocket of VEGFR2 tyrosine kinase and showed high selectivity and inhibitory potency (IC50 <1 nmol/L Therefore, it is believed that anlotinib combined with SLC might suppress tumor cell activity. The findings of the current study provided strong evidence for the combination of anlotinib and SLC in patients with NSCLC. Future studies could further compare the combination efficacy of anlotinib with different SLC.

Limitations: The study is retrospective and the sample size is limited, which may have selection bias. Additionally, the influence of the two regimens on the median survival was not compared, so the efficacy of the treatment warrants validation by more high-quality studies.

CONCLUSION

Anlotinib combined with standard chemotherapy as a SLT demonstrated effectiveness in regulating the levels of immune cells and inflammatory factors, and has a favorable short-term clinical outcome with manageable adverse reactions in patients with advanced NSCLC.

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Authors' Contributions:

ZL: Conceived and designed the study.
ZL, **XW**, **CH**, **WL** and **YJ:** Collected the data and performed the analysis.
ZL: Was involved in the writing of the manuscript and is responsible for the integrity of the study.
All authors have read and approved the final manuscript.