Efficacy and safety of anlotinib combined with vinorelbine as second-line treatment for elderly patients with advanced squamous cell lung carcinoma: A retrospective cohort

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Abstract. The aim of the present study was to investigate the efficacy and safety of anlotinib combined with vinorelbine (NVB) as a second-line treatment for elderly patients with advanced squamous cell lung carcinoma (SqCLC). The present retrospective analysis included 48 elderly patients (aged ≥65 years) diagnosed with advanced SqCLC who received anlotinib in combination with NVB as a second-line therapy between January 2021 and December 2023. The primary endpoints assessed were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and safety profile. The median PFS and OS for the cohort was found to be 5.0 and 9.5 months, respectively. By contrast, the ORR and DCR were found to be 29.17 and 70.83%. Further subgroup analysis indicated that patients who experienced specific adverse events (AEs), such as hypertension, proteinuria and hand-foot syndrome during treatment, generally had superior efficacy compared with those who did not experience these AEs (mPFS, 6.0 vs. 4.0 months; mOS, 11.0 vs. 8.5 months). In addition, apart from promising efficacy, patients who experienced common AEs also experienced decreased appetite (35.42%), fatigue (29.17%), hypertension (25%) and hand-foot syndrome (27.08%). Grade 3 or higher AEs occurred in <30% of patients, the majority of which was alleviated through corresponding support care. These results suggest that the combination of anlotinib and NVB as second-line therapy for elderly patients with advanced SqCLC demonstrated promising efficacy and a manageable safety profile. Such regimen may be a viable treatment option for this patient population. However, further prospective studies are required to validate these findings and optimize the dosing schedule for improved therapeutic outcomes.

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Introduction

Squamous cell lung carcinoma (SqCLC) constitutes a significant subset of non-small cell lung cancer (NSCLC) that is characterized by its distinctive histological features and clinical behavior (1). Despite advancements in the management of NSCLC, therapeutic options for advanced SqCLC remain limited, particularly in the elderly population. This is mainly due to the presence of multiple comorbidities and decreased tolerance to aggressive treatment methods (2). As the global population ages, the incidence of SqCLC among the elderly is expected to rise, necessitating the exploration of novel effective and tolerable second-line therapies for this demographic population (3). Elderly patients with SqCLC pose unique challenges, due to age-related physiological changes, comorbid conditions and increased susceptibility to treatment-related toxicities (4). Standard first-line therapies, which typically involve platinum-based chemotherapy, have demonstrated limited efficacy towards SqCLC and are frequently associated with severe adverse effects, which can be particularly debilitating for elderly patients (5,6). These factors underscore the need for alternative therapeutic approaches that offer a favorable balance between efficacy and safety (7,8).

Anlotinib is an oral multi-targeted tyrosine kinase inhibitor that has demonstrated promising antitumor activity in various malignancies, including NSCLC (9). It exerts its effects by inhibiting multiple pathways involved in tumor angiogenesis and proliferation, including vascular endothelial growth factor receptors, fibroblast growth factor receptors

and platelet-derived growth factor receptors. Previous clinical studies have demonstrated its efficacy in prolonging progression-free survival (PFS) and overall survival (OS) in patients with NSCLC, leading to its approval for use for advanced stages of this disease (10,11).

Vinorelbine (NVB) is a semi-synthetic vinca alkaloid that has been found to disrupt microtubule formation during cell division, which exerts cytotoxic effects on rapidly proliferating cancer cells (12). It has been extensively used for the treatment of NSCLC, both as a monotherapy (13,14) and in combination with other chemotherapeutic agents (15). In addition, the relatively mild toxicity profile of NVB compared with other chemotherapeutics renders it a viable option for elderly patients who may not tolerate more aggressive regimens (16,17).

Combining targeted therapies such as anlotinib with traditional chemotherapeutic agents, such as NVB, represents a strategic approach to enhance therapeutic efficacy whilst potentially mitigating the dose-limiting toxicities associated with single-agent therapy (18-20). The rationale for this combination stems from their complementary mechanisms of action, where anlotinib can inhibit key pathways in tumor growth and angiogenesis, whilst NVB directly targets the cell cycle. This dual approach may theoretically result in improved tumor control by attacking the cancer through different biological pathways (21,22). A previous study highlighted the benefits of anlotinib in NSCLC, demonstrating significant improvements in PFS and OS (9). However, to the best of the authors' knowledge, there is a paucity of data specifically addressing the combination of anlotinib and NVB in the context of second-line treatment for elderly patients with advanced SqCLC. Given the distinct biological behavior of SqCLC and the specific considerations required for treating elderly patients, there is a critical need to evaluate the efficacy and safety of this combination therapy. Therefore, the present study aimed to fill the existing knowledge gap by investigating the clinical outcomes and safety profile of anlotinib combined with NVB as a second-line treatment in elderly patients with advanced SqCLC.

Patients and methods

Study design. The present study was a retrospective, multicenter study conducted on elderly patients (aged ≥65 years; male-to-female sex ratio is ~3:2) with advanced SqCLC who have previously failed first-line treatment. The study protocol was approved (approval no. HBCHEC2021108) by the Institutional Review Board Hubei Cancer Hospital, affiliated with Tongji Medical College (Wuhan, China), Since this is a retrospective study, the informed consent was waived. Patient selection criteria was as follows: i) Age, ≥65 years; ii) histologically confirmed advanced SqCLC; iii) previous failure of first-line treatment; iv) Eastern Cooperative Oncology Group performance status of 0-2; v) adequate organ function; and vi) absence of other active malignancies or medical conditions that may affect treatment outcomes. Key exclusion criteria included previous treatment included antitumor angiogenesis therapy and chemotherapy with vincristine-containing regimens, symptomatic brain metastasis, cachexia and the expectancy life of <3 months.

Table I. Baseline clinical characteristics of the study cohort.

Characteristics	No. of patients (%)
Age	
Years	72
Range	65-80
Sex	
Male	28 (58.33%)
Female	20 (41.67%)
Smoking history	
Never smoker	15 (31.25%)
Former smoker	33 (68.75%)
ECOG score	
0-1	36 (75.00%)
≥2	12 (25.00%)
Previous radiotherapy	
Yes	12 (25.00%)
No	36 (75.00%)
Brain metastasis	
Measurable	11 (22.92%)
Unmeasurable	37 (77.08%)
Bone metastasis	
Yes	34 (70.83%)
No	14 (29.17%)
Liver metastasis	
Yes	8 (16.67%)
No	40 (83.33%)
Stage	
IVA	7 (14.58%)
IVB	19 (39.58%)
IVC	22 (45.83%)
Metastasis type	
Multi-site metastases	39 (81.25%)
Oligo-metastases	9 (18.75%)
PD-L1 expression	
PD-L1(+)	4 (8.34%)
PD-L1(-)	10 (20.83%)
Unknown	34 (70.83%)
Comorbidities	
Yes	15 (31.25%)
No	33 (68.75%)

PD-L1, programmed cell death-ligand 1.

Treatment administration. Elderly patients with advanced SqCLC who progressed after first-line chemotherapy received treatment with anlotinib combined with oral NVB. Patients received anlotinib orally at a standard dose of 12 mg once daily on days 1-14 of a 21-day cycle. If adverse reactions are severe, the dose can be sequentially reduced to 10 or 8 mg. If 8 mg cannot be tolerated, permanent discontinuation of the drug would be considered. NVB is available in capsule

Table II. Clinical Activity of Anlotinib plus NVB in advanced older cell lung carcinoma.

	Patient no.	Ratio
Complete response	0	0
Partial response	14	29.17% (14/48)
Stable response	20	41.66% (20/48)
Progressive disease	14	29.17% (14/48)
Objective response		29.17%
Disease control rate		70.83%
Median progression-free survival		5.0 months
Median overall survival		9.5 months

form for oral administration at a dose of 60 mg/m^2 once a week. If adverse reactions are intolerable, the dose can be sequentially reduced to 40 mg/m^2 and then to 20 mg/m^2. If the 20 mg/m^2 dose remains intolerable, permanent discontinuation of the drug would be recommended. Each cycle of administration lasted 3 weeks, with treatment continuing until disease progression or the occurrence of intolerable toxic side effects.

Assessment of efficacy and safety. The primary endpoints for efficacy evaluation are OS, PFS, objective response rate (ORR) and disease control rate (DCR). OS was the primary endpoint in the present study, which was measured from the date of treatment initiation until the patient succumbed to disease from any cause or last follow-up. PFS was defined from treatment initiation to disease progression, based on RECIST criteria or mortality. ORR was defined as the proportion of patients achieving complete response (CR) or partial response (PR) according to RECIST criteria. DCR was defined as the proportion of patients achieving CR, PR or stable disease for ≥12 weeks according to RECIST criteria. Adverse events (AEs) were assessed according to the Common Terminology Criteria for AEs version 5.0. Laboratory assessments, vital signs monitoring and physical examinations were performed regularly, before they were used to classify the severity of adverse reactions for adequate management during treatment through dose reduction and symptomatic supportive care.

Statistical analysis. Descriptive statistics were used to summarize patient demographics, baseline characteristics and treatment compliance. Kaplan-Meier curves were applied to estimate OS and PFS. Subgroup comparisons were conducted using the log-rank test. The ORR and DCR were reported with corresponding confidence intervals. Safety profiles were presented as frequency and percentage of AEs. Data were statistically analyzed using SPSS 13.0 software, and graphs were generated using GraphPad Prism 5.0 Software (Dotmatics). A P-value of less than 0.05 was considered statistically significant. The database used in the present study can be accessed at the following URL: https://kmplot.com/analysis/index.php?p=service&cancer=lung.

Table III. Adverse events of anlotinib plus NVB in advanced older cell lung carcinoma.

	Anlotinib plus NVB (n (%))	
Adverse event	Any grade	Grade 3 or 4
Hematological		
Leukopenia	9 (18.75%)	2 (4.17%)
Neutropenia	8 (16.67%)	2 (4.17%)
Anemia	7 (14.58%)	0%
Thrombocytopenia	7 (14.58%)	0%
Non-hematological		
Peripheral neuropathy	10 (20.83%)	1 (2.08%)
Hypertension	12 (25.00%)	3 (6.25%)
Hand-foot syndrome	13 (27.08%)	2 (4.17%)
Proteinuria	11 (22.92%)	2 (4.17%)
Elevated transaminase	6 (12.50%)	1 (2.08%)
Hyperbilirubinemia	2 (4.17%)	0%
Bleeding	0%	0%
Fatigue	14 (29.17%)	0%
ALP increased	2 (4.17%)	0%
Elevated gamma-glutamyl transpeptidase	3 (6.25%)	0%
Abdominal pain	4 (8.33%)	0%
Decreased appetite	17 (35.42%)	0%
Hypoproteinemia	3 (6.25%)	0%
Diarrhea	4 (8.33%)	0%
Elevated lactate dehydrogenase	2 (4.17%)	0%
Oral ulcer	5 (10.42%)	0%
Stomatitis	6 (12.50%)	0%
Dysphagia	4 (8.33%)	0%
Dysphonia	3 (6.25%)	0%
Rash	2 (4.17%)	0%

NVB, vinorelbine.

Results

Patient demographics and baseline characteristics. The present study enrolled 48 elderly patients (aged ≥65 years) with advanced SqCLC who had previously failed first-line treatment. The median age of the patients was 72 years (range, 65-80 years), with a male predominance (58.33%). The patient performance status scores ranged from 0 to 2, with 75% of patients scoring 0 or 1 and 25% scoring 2. Baseline comorbidities (Table I) included hypertension (21%), diabetes mellitus (15%) and chronic obstructive pulmonary disease (18%). The proportions of patients with multiple metastases and oligo-metastases were 81.25 and 18.75%, respectively. In addition, the majority of patients had unknown PD-L1 expression status (70.83%), with only a small proportion (<30%) undergoing PD-L1 testing on re-biopsy specimens. Among these patients, the proportions of those with PD-L1 ≥1% and PD-L1 <1% were 8.34 and 20.83%, respectively. After disease

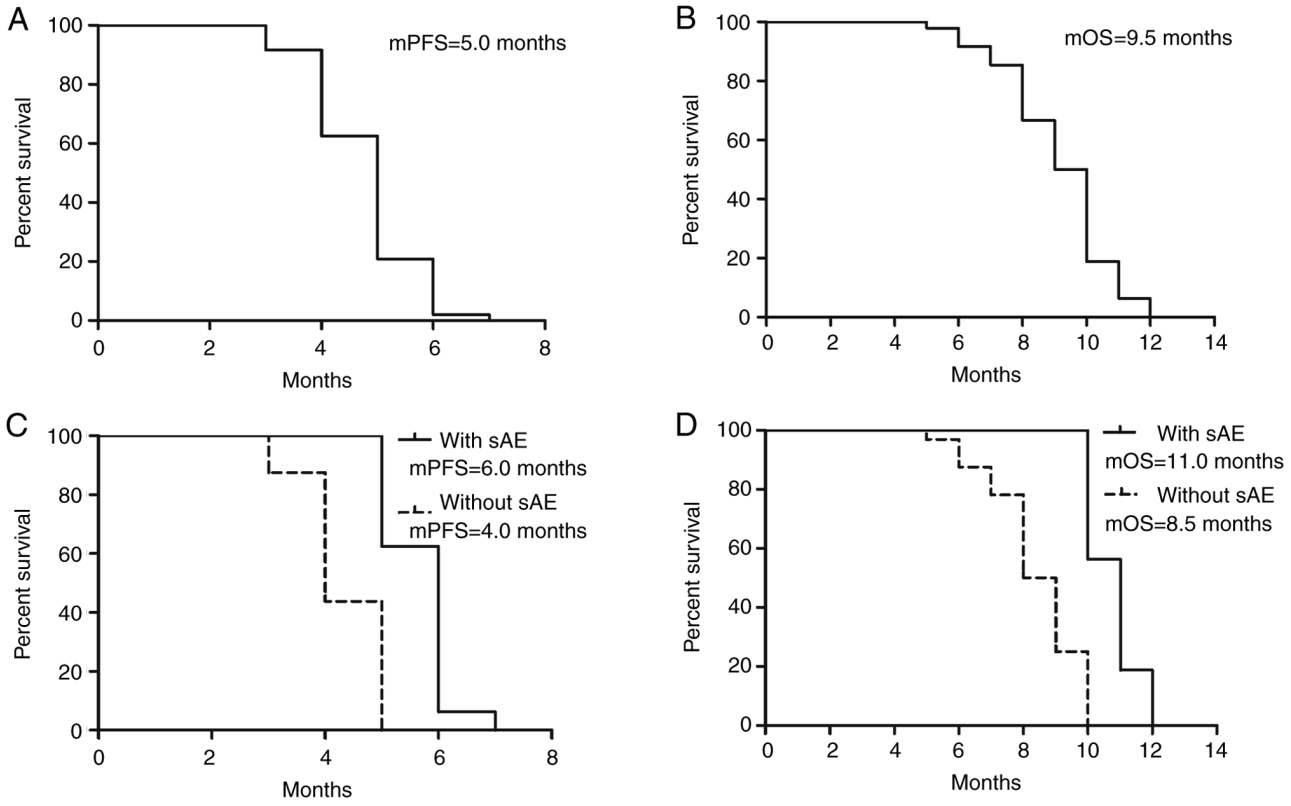

Figure 1. PFS and OS analysis of the general population and subgroup of elderly patients with advanced SqCLC who accepted the drug combination of anlotinib and vinorelbine. (A) PFS and (B) OS in the present study. Comparisons of (C) PFS and (D) OS between these patients with sAE and without sAE. PFS, progression-free survival; OS, overall survival; SqCLC, squamous cell lung carcinoma; sAE, specific adverse event (such as proteinuria, hypertension or hand-foot syndrome); m, median.

progression, <30% of patients received third-line treatment, with the treatment regimen determined by clinicians based on the individual patient's condition.

Efficacy outcomes. Preliminary results indicated that the median PFS and OS for the drug combination of anlotinib and NVB in the second line treatment of advanced SqCLC was 5.0 and 9.5 months, respectively. In addition, the ORR was 29.17%, suggesting an improvement compared with historical controls receiving single-agent or best supportive care. Additionally, DCR was 70.83% (Table II). This high rate of disease control indicates that the combination regimen was effective in managing tumor growth in the majority of patients (Fig. 1; Table I).

Safety and tolerability. The safety profile of the anlotinib-NVB combination was consistent with known toxicities of the individual agents, but no unexpected AEs were observed. Common hematological toxicities of the regimen include leukopenia, neutropenia, anemia and thrombocytopenia. Common non-hematological toxicities include fatigue, decreased appetite, hypertension, proteinuria and hand-foot syndrome, primarily of grade 1-2 severity. The incidence of severe toxicities (grade 3 or higher) did not exceed 30% (Table III). Dose modifications were required in 24% patients due to AEs, primarily involving NVB. Additionally, the proportion of patients who discontinued treatment due to severe adverse reactions was 11%. Despite AEs, the overall tolerability was deemed acceptable, particularly given the advanced age and comorbidity burden of the patient population. Supportive care measures, including dose modifications and symptomatic treatments, successfully managed the majority of side effects.

Subgroup analysis. To further identify the beneficial patient population for this treatment regimen, a subgroup analysis was conducted. The results revealed that patients who experienced specific AEs during treatment (mainly hypertension, proteinuria and hand-foot syndrome) generally had superior efficacy compared with those who did not experience these AEs [mPFS, 6.0 vs. 4.0 months; hazard ratio (HR), 1.500; 95% confidence interval (CI), 0.9513-2.049; P<0.0001; mOS, 11.0 vs. 8.5 months; HR, 1.294; 95% CI, 0.7454-1.843; P<0.0001; Fig. 1]. This suggests that recognizing these toxicities during treatment may serve as potential markers for predicting treatment efficacy (Fig. 1; Table I).

Discussion

The treatment of advanced SqCLC in elderly patients presents substantial challenges due to the typically poor performance status and comorbidities associated with this population (2,3). Traditional chemotherapy regimens frequently result in significant toxicity, which can outweigh the benefits in frail patients (23). Therefore, it is crucial to identify novel therapeutic strategies that are both effective and tolerable for elderly individuals (4).

Based on the current drug treatment models, combination therapy is likely to become a trend in future treatment development (24-26). From the perspective of efficacy and tolerability, the combination of anlotinib with metronomic chemotherapy using NVB has demonstrated significant potential for application in elderly patients with advanced SqCLC (19,27). However, to the best of the authors' knowledge, there are currently no similar research reports available (28). The present study primarily enrolled elderly patients with advanced SqCLC. This decision was based on existing research suggesting that age can serve as an independent prognostic factor (29), a finding also supported by data in the diagnosis and treatment of SqCLC (30). However, there is still some debate in the academic community regarding the definition of 'elderly' (31). Taking into account the specific context of China (32,33) and referring to relevant literature, in the present study 'elderly' was defined as individuals aged ≥65 (34-36).Consistent with previous studies, the present results demonstrated a notable improvement in ORR and PFS with the combination therapy compared with historical controls receiving NVB monotherapy or best supportive care (13,14,27). Specifically, the ORR reached ~30%, which is encouraging given the typically low response rates in this patient cohort. The median PFS was extended to 5.0 months, suggesting a meaningful delay in disease progression. These outcomes are particularly significant in the context of treating elderly patients, who typically have limited therapeutic options and lower tolerance for aggressive treatments. Median OS was observed at 9.5 months, representing a positive trend compared with existing second-line treatments for this demographic population (7,16,37). Furthermore, the present study included a portion of patients with a performance status of 2 (accounting for 25% of the cohort), in order to reflect the treatment needs of elderly patients with advanced SqCLC (38,39). These patients have their own characteristics, such as being often excluded from enrollment in previous clinical studies, having poor tolerance to intravenous chemotherapy, and suffering from multiple comorbidities such as hypertension, diabetes and chronic obstructive pulmonary disease. They also lack treatment options, and the efficacy is limited. Therefore, from both the efficacy and safety perspectives, this population is likely to represent a clinical application advantage of this regimen (40,41). Additionally, the efficacy of this regimen was found to be associated with the occurrence of specific AEs (hypertension, proteinuria and hand-foot syndrome), suggesting that the identification of these toxicities can serve as potential markers for predicting treatment efficacy (42,43).

Safety and tolerability are crucial considerations in the elderly population. The AEs observed in the present study were consistent with the known profiles of anlotinib (44,45) and NVB (46,47). Common AEs included fatigue, hypertension, hand-foot syndrome and neutropenia. Importantly, the majority of these AEs were manageable and reversible. Dose reductions and supportive care measures were effective in mitigating severe toxicities, allowing for the majority of patients to continue treatment without interruption (46). Notably, no new or unexpected safety signals emerged during the study period.

The combination of anlotinib and NVB appeared to have provided a balance between efficacy and safety. The dual approach targets both angiogenesis and cell division, potentially overcoming resistance mechanisms that limit the effectiveness of monotherapies (22,48-50). In addition, the favorable safety profile supports the feasibility of this regimen in elderly patients, who are frequently excluded from clinical trials due to concerns about toxicity (2). Several factors may have contributed to the observed benefits of this combination therapy. Anlotinib's multi-targeted approach can effectively disrupt angiogenic signaling, which is critical in SqCLC pathogenesis (51,52). In addition, NVB's ability to induce mitotic arrest may have complemented anlotinib's anti-angiogenic effects, enhancing overall antitumor activity (22,53,54). The oral administration of anlotinib and NVB can also provide convenience and flexibility, improving adherence in the elderly population (13,14,55). However, certain limitations must be acknowledged. The present study's sample size was relatively small and the single-arm design limits direct comparisons with other treatment modalities. Additionally, although subgroup analysis revealed a statistical difference in efficacy between patients who did not experience hypertension, proteinuria, hand-foot syndrome, and those who did, the 95% CI was within 1 (with sAE vs. without sAE; mPFS 6.0 months vs. 4.0 months; HR=1.500, 95% CI=0.9513-2.049; P<0.0001; mOS 11.0 months vs. 8.5 months; HR=1.294, 95% CI, 0.7454-1.843; P<0.0001). This raises the question of whether this result is due to an insufficient sample size in the present study, or whether there is inherently little difference in efficacy between these two groups. Alternatively, it may suggest that using treatment-related AEs as a predictor of efficacy is not a reliable indicator, which is clearly an issue worth further exploration. Future randomized controlled trials with larger cohorts are necessary to validate these findings and determine the optimal sequencing and dosing strategies for anlotinib and NVB in this setting (25,48,56,57).

In conclusion, anlotinib combined with NVB demonstrated promise as a second-line treatment for elderly patients with advanced SqCLC, offering improved efficacy and a manageable safety profile. This combination represents a viable therapeutic option, addressing the unmet need for effective and tolerable treatments in this vulnerable population. Ongoing research and clinical trials should further elucidate the potential of this regimen and refine its role in the management of advanced SqCLC (1,58).

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YoL and WL were responsible for data analysis and interpretation. YiL and YP collected the data. JT and XL conceptualized and designed the study. All authors read and approved the final version of the manuscript. JT and XL confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study complied with the principles outlined in the Declaration of Helsinki (revised in 2013). Ethical approval (approval no. HBCHEC2021108) for this retrospective trial was obtained from the Ethics Committee of Hubei Cancer Hospital, affiliated with Tongji Medical College (Wuhan, China). Since this is a retrospective study, the informed consent was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Hsu EC, Wu KL, Tsai YM, Lee MH, Tsai MJ, Kuo CY, Liu YC, Liang FW, Yang CJ and Hung JY: Real-world treatment pattern and prognostic factors of stage IV lung squamous cell carcinoma patients. Kaohsiung J Med Sci 38: 1001-1011, 2022.
2. Ganti AK, Klein AB, Cotarla I, Seal B and Chou E: Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. JAMA Oncol 7: 1824-1832, 2021.
3. Santos ES and Rodriguez E: Treatment considerations for patients with advanced squamous cell carcinoma of the lung. Clin Lung Cancer 23: 457-466, 2022.
4. Basnet A, Alahmadi A and Gajra A: Older patients with lung cancer: A summary of seminal contributions to optimal patient care. Curr Oncol Rep 24: 1607-1618, 2022.
5. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, Rodríguez-Cid J, Tafreshi A, Cheng Y, Lee KH, *et al*: Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the phase III KEYNOTE-407 Study. J Clin Oncol 41: 1999-2006, 2023.
6. Uprety D, Remon J and Peters S: First-line dual immunotherapy, a treatment option in first-line metastatic non-small-cell lung cancer: Are we ready to use it? J Clin Oncol 42: 378-382, 2024.
7. Lau SCM, Pan Y, Velcheti V and Wong KK: Squamous cell lung cancer: Current landscape and future therapeutic options. Cancer Cell 40: 1279-1293, 2022.
8. Filipits M: New developments in the treatment of squamous cell lung cancer. Curr Opin Oncol 26: 152-158, 2014.
9. Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Zhao Y, *et al*: Effect of anlotinib as a third-line or further treatment on overall survival of patients with advanced non-small cell lung cancer: The ALTER 0303 phase 3 randomized clinical trial. JAMA Oncol 4: 1569-1575, 2018.
10. Zhang C, Kong FW, Wu WB, Zhang M, Yu GM, Wang X and Liu YY: First-line pemetrexed and carboplatin plus anlotinib for epidermal growth factor receptor wild-type and anaplastic lymphoma kinase-negative lung adenocarcinoma with brain metastasis: A case report and review of the literature. Medicine (Baltimore) 99: e22128, 2020.
11. Jiang S, Liang H, Liu Z, Zhao S, Liu J, Xie Z, Wang W, Zhang Y, Han B, He J and Liang W: The impact of anlotinib on brain metastases of non-small cell lung cancer: Post Hoc Analysis of a Phase III Randomized Control Trial (ALTER0303). Oncologist 25: e870-e874, 2020.
12. Capasso A: Vinorelbine in cancer therapy. Curr Drug Targets 13: 1065-1071, 2012.
13. Bilir C, Durak S, Kızılkaya B, Hacıbekiroglu I, Nayır E and Engin H: Efficacy of metronomic vinorelbine in elderly patients with advanced non-small-cell lung cancer and poor performance status. Curr Oncol 24: e199-e204, 2017.
14. Platania M, Pasini F, Porcu L, Boeri M, Verderame F, Modena Y, Del Conte A, Nichetti F, Garassino MC, Martinetti A, *et al*: Oral maintenance metronomic vinorelbine versus best supportive care in advanced non-small-cell lung cancer after platinum-based chemotherapy: The MA.NI.LA. multicenter, randomized, controlled, phase II trial. Lung Cancer 132: 17-23, 2019.
15. Grossi F, Jaśkiewicz P, Ferreira M, Czyżewicz G, Kowalski D, Ciuffreda L, Garcia-Gomez R, Caruso S, Bosch-Barrera J, Gautier S, *et al*: Oral vinorelbine and cisplatin as first-line therapy for advanced squamous NSCLC patients: A prospective randomized international phase II study (NAVoTrial 03). Ther Adv Med Oncol 13: 17588359211022905, 2021.
16. Rossi D, Lippe P, Rocchi MBL, Sarti D, Catalano V, Graziano F, Giordani P, Baldelli A, Fedeli SL, Imperatori L, *et al*: Metronomic oral vinorelbine: an alternative schedule in elderly and patients PS2 with local/advanced and metastatic NSCLC Not Oncogene-addicted. In Vivo 34: 2687-2691, 2020.
17. D'Ascanio M, Pezzuto A, Fiorentino C, Sposato B, Bruno P, Grieco A, Mancini R and Ricci A: Metronomic chemotherapy with vinorelbine produces clinical benefit and low toxicity in frail elderly patients affected by advanced non-small cell lung cancer. Biomed Res Int 2018: 6278403, 2018.
18. Xiang M, Yang X, Ren S, Du H, Geng L, Yuan L, Wen Y, Lin B, Li J, Zhang Y, *et al*: Anlotinib combined with S-1 in third- or later-line stage IV non-small cell lung cancer treatment: A phase II clinical trial. Oncologist 26: e2130-e2135, 2021.
19. Li DD, Tao ZH, Wang BY, Wang LP, Cao J, Hu XC and Zhang J: Apatinib plus vinorelbine versus vinorelbine for metastatic triple-negative breast cancer who failed first/second-line treatment: the NAN trial. NPJ Breast Cancer 8: 110, 2022.
20. Huang JY, Chen XL, Xie XF, Song L, Chen LP, Lan XF, Bai X, Chen X and Du CW: The efficiency and safety of low-dose apatinib combined with oral vinorelbine in pretreated HER2-negative metastatic breast cancer. Cancer Med 13: e7181, 2024.
21. Xu H, Lv D, Meng Y, Wang M, Wang W, Zhou C, Zhou S, Chen X and Yang H: Endostar improved efficacy of concurrent chemoradiotherapy with vinorelbine plus carboplatin in locally advanced lung squamous cell carcinoma patients with high serum Lp(a) concentration. Ann Palliat Med 9: 298-307, 2020.
22. Ito K, Hamamichi S, Abe T, Akagi T, Shirota H, Kawano S, Asano M, Asano O, Yokoi A, Matsui J, *et al*: Antitumor effects of eribulin depend on modulation of the tumor microenvironment by vascular remodeling in mouse models. Cancer Sci 108: 2273-2280, 2017.
23. Liao BC, Shao YY, Chen HM, Shau WY, Lin ZZ, Kuo RN, Lai CL, Chen KH, Cheng AL, Yang JC and Lai MS: Comparative effectiveness of first-line platinum-based chemotherapy regimens for advanced lung squamous cell carcinoma. Clin Lung Cancer 16: 137-143, 2015.
24. Li X, Wu D, Tang J and Wu Y: The efficiency and safety of triple-drug combination of albumin-bound paclitaxel, anlotinib and PD-1/L1 Inhibitors in the 2(nd) or above line of advanced NSCLC: A retrospective cohort study. Cancer Manag Res 16: 1003-1012, 2024.
25. Tang J, Jiang H, Xiang Z, Zhu X, Xie R, Wu D, Peng L and Li X: Apatinib plus docetaxel or pemetrexed shows promising activities against non-small cell lung cancer with brain metastasis: A retrospective analysis. J Thorac Dis 16: 615-622, 2024.
26. Yin C, Zou GR, He Y, Li J, Yan HW, Su Z, Cao XL and Li XB: Efficiency and toxicity of nab-paclitaxel and camrelizumab in the second or above line treatment of advanced non-small cell lung cancer: A retrospective cohort study. J Thorac Dis 15: 1838-1847, 2023.
27. Wang L, He Z, Yang S, Tang H, Wu Y, Li S, Han B, Li K, Zhang L, Shi J, *et al*: The impact of previous therapy strategy on the efficiency of anlotinib hydrochloride as a third-line treatment on patients with advanced non-small cell lung cancer (NSCLC): A subgroup analysis of ALTER0303 trial. Transl Lung Cancer Res 8: 575-583, 2019.

28. Zhang X, Xiong Y, Xia Q, Wu F, Liu L, Zhou Y, Zeng L, Zhou C, Xia C, Jiang W, *et al*: Efficacy and safety of apatinib plus vinorelbine in patients with wild-type advanced non-small cell lung cancer after second-line treatment failure: A nonrandomized clinical trial. JAMA Netw Open 3: e201226, 2020.
29. Howard FM and Pearson AT: Prognosis and treatment of non-small cell lung cancer in the age of deep learning. JAMA Netw Open 3: e206368, 2020.
30. Kukulj S, Aukst Margetic B, Jakovljevic M and Samarzija M: Temperament and character and quality of life in lung cancer patients. Tumori 99: 708-714, 2013.
31. Okamoto J, Kubokura H and Usuda J: Factors determining the choice of surgical procedure in elderly patients with non-small cell lung cancer. Ann Thorac Cardiovasc Surg 22: 131-138, 2016.
32. Chen K, Yang D, Li F, Gao L, Tian Y, Xu B, Xu X, Xu Q and Cao J: Changes in the symptom clusters of elderly patients with lung cancer over the course of postoperative rehabilitation and their correlation with frailty and quality of life: A longitudinal study. Eur J Oncol Nurs 67: 102388, 2023.
33. She J, Yang P, Hong Q and Bai C: Lung cancer in China: Challenges and interventions. Chest 143: 1117-1126, 2023.
34. Kwan SW, Mortell KE, Talenfeld AD and Brunner MC: Thermal ablation matches sublobar resection outcomes in older patients with early-stage non-small cell lung cancer. J Vasc Interv Radiol 25: 1-9.e1, 2014.
35. Fang Z, He J, Fang W, Ruan L and Fang F: Long-term outcomes of thoracoscopic anatomic resections and systematic lymphadenectomy for elderly high-risk patients with stage IB non-small-cell lung cancer. Heart Lung Circ 25: 392-397, 2016.
36. Ye X, Liu Y, Yang J, Wang Y, Cui X, Xie H, Song L, Ding Z, Zhai R, Han Y, *et al*: Do older patients with stage IB non-small-cell lung cancer obtain survival benefits from surgery? A propensity score matching study using SEER data. Eur J Surg Oncol 48: 1954-1963, 2022.
37. Lee SM, Schulz C, Prabhash K, Kowalski D, Szczesna A, Han B, Rittmeyer A, Talbot T, Vicente D, Califano R, *et al*: First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): A phase 3, global, multicentre, open-label, randomised controlled study. Lancet 402: 451-463, 2023.
38. Sun L, Zhao Q, Wang Y, Wang Y, Zheng M, Ding X and Miao L: Efficacy and safety of anlotinib-containing regimens in advanced non-small cell lung cancer: A real-world study. Int J Gen Med 16: 4165-4179, 2023.
39. Kokkotou E, Anagnostakis M, Evangelou G, Syrigos NK and Gkiozos I: Real-world data and evidence in lung cancer: A review of recent developments. Cancers (Basel) 16: 1414, 2024.
40. Nobili S, Lavacchi D, Perrone G, Vicini G, Tassi R, Landini I, Grosso A, Roviello G, Mazzanti R, Santomaggio C and Mini E: Vinorelbine in non-small cell lung cancer: Real-World data from a single-institution experience. Oncol Res 28: 237-248, 2020.
41. Wang M, Mao M, Yang Y, Cai Z, Li Y, Chen Y, Cai J and Ye Q: Safety and efficacy of anlotinib hydrochloride capsules in advanced non-small-cell lung cancer: A multicenter, real-world study. Future Oncol 19: 1729-1739, 2023.
42. Wei W, Ban X, Yang F, Li J, Cheng X, Zhang R, Huang X, Huang Y, Li Q, Qiu Y, *et al*: Phase II trial of efficacy, safety and biomarker analysis of sintilimab plus anlotinib for patients with recurrent or advanced endometrial cancer. J Immunother Cancer 10: e004338, 2022.
43. Jiang M, Zhang C, Hu Y, Li T, Yang G, Wang G, Zhu J, Shao C, Hou H, Zhou N, *et al*: Anlotinib combined with toripalimab as second-line therapy for advanced, relapsed gastric or gastro-esophageal junction carcinoma. Oncologist 27: e856-e869, 2022.
44. Alshangiti A, Chandhoke G and Ellis PM: Antiangiogenic therapies in non-small-cell lung cancer. Curr Oncol 25 (Suppl 1): S45-S58, 2018.
45. Si X, Zhang L, Wang H, Zhang X, Wang M, Han B, Li K, Wang Q, Shi J, Wang Z, *et al*: Management of anlotinib-related adverse events in patients with advanced non-small cell lung cancer: Experiences in ALTER-0303. Thorac Cancer 10: 551-556, 2019.
46. Carlson K and Ocean AJ: Peripheral neuropathy with microtubule-targeting agents: Occurrence and management approach. Clin Breast Cancer 11: 73-81, 2011.
47. Noguchi E and Maeda Y: Chemotherapy-induced peripheral neuropathy. Gan To Kagaku Ryoho 38: 1773-1776, 2011 (In Japanese).
48. Xu B, Sun T, Wang S and Lin Y: Metronomic therapy in advanced breast cancer and NSCLC: Vinorelbine as a paradigm of recent progress. Expert Rev Anticancer Ther 21: 71-79, 2021.
49. Li X, Peng Y, Wu D, Tang J and Wu Y: Efficacy and safety of anlotinib as maintenance therapy in patients with advanced non-small cell lung cancer achieving SD post first-line chemotherapy combined with immunotherapy. J Chemother: Sep 1, 2024 (Epub ahead of print).
50. Glorieux C, Xia X, You X, Wang Z, Han Y, Yang J, Noppe G, Meester C, Ling J, Robert A, *et al*: Cisplatin and gemcitabine exert opposite effects on immunotherapy with PD-1 antibody in K-ras-driven cancer. J Adv Res 40: 109-124, 2022.
51. Blumberg N: Tumor angiogenesis factor. Speculations on an approach to cancer chemotherapy. Yale J Biol Med 47: 71-81, 1974.
52. Cabebe E and Wakelee H: Role of anti-angiogenesis agents in treating NSCLC: Focus on bevacizumab and VEGFR tyrosine kinase inhibitors. Curr Treat Options Oncol 8: 15-27, 2007.
53. Zhang Y, Yang SH and Guo XL: New insights into Vinca alkaloids resistance mechanism and circumvention in lung cancer. Biomed Pharmacother 96: 659-666, 2017.
54. Laquente B, Viñals F and Germà JR: Metronomic chemotherapy: An antiangiogenic scheduling. Clin Transl Oncol 9: 93-98, 2007.
55. Wang J, Li X, Zhou J, Qiu D, Zhang M, Sun L and Li SC: Long-term survival with anlotinib as a front-line treatment in an elderly NSCLC patient: A case report. Front Oncol 13: 1043244, 2023.
56. Qiang H, Chang Q, Xu J, Qian J, Zhang Y, Lei Y, Han B and Chu T: New advances in antiangiogenic combination therapeutic strategies for advanced non-small cell lung cancer. J Cancer Res Clin Oncol 146: 631-645, 2020.
57. Li X, Wu D, Tang J and Wu Y: The efficiency and safety of temozolomide and PD-1/L1 inhibitors in pretreated NSCLC with brain metastasis: A retrospective cohort. J Cancer Res Clin Oncol 150: 271, 2024.
58. Niu Z, Jin R, Zhang Y and Li H: Signaling pathways and targeted therapies in lung squamous cell carcinoma: Mechanisms and clinical trials. Signal Transduct Target Ther 7: 353, 2022.