

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.

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

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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, multi-center study conducted on elderly patients (aged ≥ 65 years; male-to-female sex ratio is $\sim 3:2$) 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/m² once a week. If adverse reactions are intolerable, the dose can be sequentially reduced to 40 mg/m² and then to 20 mg/m². If the 20 mg/m² 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

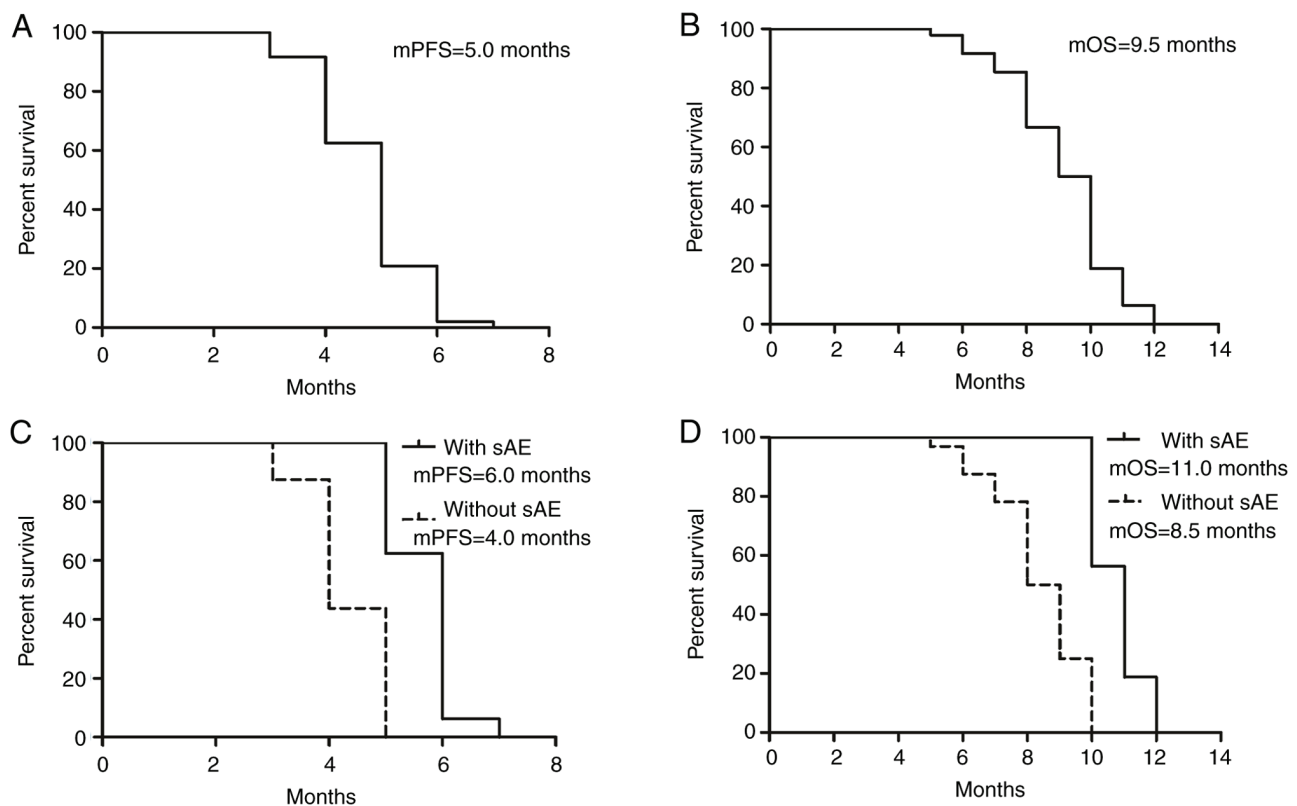


Figure 1. PFS and OS analysis of the general population and subgroup of elderly patients with advanced SqCLC who accepted the drug combination of anlotinib and vinorelbine. (A) PFS and (B) OS in the present study. Comparisons of (C) PFS and (D) OS between these patients with sAE and without sAE. PFS, 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 $\sim 30\%$, 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.

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