Original Article

Efficacy and outcome analysis: monotherapy and combination therapy of S-1 for patients with advanced non-small cell lung cancer

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Background: Lung cancer is the leading cause of cancer-related mortality worldwide. S-1, a fluorouracil derivative known for its efficacy and minimal adverse effects in various solid tumors, offers hope for advanced non-small cell lung cancer (NSCLC) patients. This study conducted a retrospective, single-center analysis to investigate the effectiveness and safety of S-1 monotherapy and combination therapy as second-line or subsequent treatment for advanced NSCLC.

Methods: A total of 52 patients diagnosed with advanced NSCLC at Zhejiang Cancer Hospital (Hangzhou, China) from January 1, 2018, to August 31, 2023 were included in a retrospective study. Among these patients, 13 received S-1 monotherapy while 39 received S-1 in combination therapy. The study aimed to analyze the short-term efficacy, long-term outcome, prognostic factors, and treatment-related adverse events (AEs).

Results: The objective response rate (ORR) was 28.8%, with a median progression-free survival (PFS) of 2.7 months [95% confidence interval (CI): 2.1–2.8] and a median overall survival (OS) of 9.5 months (95% CI: 6.3–12.6) for the entire cohort. The combination therapy with S-1 was determined to be a significant independent predictor of OS, while treatment line was identified as an independent negative prognostic factor for OS. The most prevalent AE observed was anemia, affecting 12 patients (23.1%). The majority of AEs were classified as grade 1–2, with only 3 patients (5.7%) experiencing grade 3–4 AEs. Further prospective studies are recommended to fully assess the therapeutic value of this treatment approach.

Conclusions: Results indicated that both S-1 monotherapy and combination therapy showed promising efficacy and were well tolerated as second-line or later-line treatments for patients with advanced NSCLC. Further prospective studies are recommended to fully assess the therapeutic value of this treatment approach.

Keywords: Immune checkpoint inhibitors (ICIs); second-line treatment; non-small cell lung cancer (NSCLC); S-1

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide. There were an estimated 2.3 million new cases and 1.2 million deaths in the United States in 2024, representing approximately 11.7% of cancers diagnosed and 20.4% of deaths (1). Non-small cell lung cancer (NSCLC) constitutes approximately 80% of all lung cancer cases in humans and is frequently detected at an advanced stage, resulting in limited treatment options (2). Although targeted and immunotherapies have advanced in recent years, advanced NSCLC still has a poor prognosis. Patients whose disease has advanced following initial treatment face a scarcity of alternative medications. For individuals with NSCLC lacking oncogenic driver mutations who have experienced progression after initial therapy, the standard treatment options include immune checkpoint inhibitor (ICI) or gemcitabine and docetaxel monotherapy or docetaxel plus ramucirumab (3), with a median progression-free survival (PFS) of only 3 months (4,5). However, not all patients can tolerate subsequent chemotherapy regimens, such as patients with a performance status (PS) ≥2. Moreover, significant adverse effects such as bone marrow suppression and fatigue are observed in patients treated with gemcitabine or docetaxel. Additionally, the incidence of grade ≥3 pneumonitis is found to be elevated in relation to the combined treatment of docetaxel and ramucirumab. In the context of the ALTER-0303 trial, anlotinib demonstrated enhanced efficacy as a third-line or subsequent therapy for patients with advanced NSCLC (6). Nevertheless, there was a significant increase in grade 3 or higher adverse reactions with anlotinib (61.9% *vs.* 37.1%). The therapeutic effects in the second-line or later-line treatment remained unsatisfactory, therefore highly efficient and low-toxic therapeutic strategies are urgently required.

S-1, an oral prodrug of fluorouracil, is administered in combination with tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate at specific molar ratios (1:0.4:1) (7). CDHP increases 5-fluorouracil (5-FU) levels in tumor tissues and plasma by generating 5-FU in the blood. By inhibiting the phosphorylation of 5-FU in the gastrointestinal tract, oxonate reduces the gastrointestinal toxicity of 5-FU. The comparative effectiveness of S-1 monotherapy *vs.* a docetaxel regimen was assessed in two randomized phase III trials to establish non-inferiority (8,9). Neither PFS nor overall survival (OS) differed significantly between S-1 oral and docetaxel regimens, indicating non-inferiority of S-1. It was found that compared with docetaxel, S-1 had similar anti-tumor activity but milder hematologic adverse effects. Furthermore, S-1 combination therapy exhibited favorable anti-tumor activity in patients with advanced NSCLC at later stages of disease progression (10-12). Given the limited treatment options available for late-stage NSCLC patients with compromised physical functions, multiple underlying diseases, and high PS scores, the potential of S-1 as a breakthrough therapy is significant (13). Furthermore, NSCLC treatment with S-1 was approved in Japan in 2004.

This study sought to investigate the efficacy and safety of S-1 combination therapy in advanced NSCLC patients as a second-line or later treatment option, as well as comparing its effectiveness with S-1 monotherapy. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-940/rc).

Highlight box

Key findings

- Both S-1 monotherapy and combination therapy demonstrated favorable efficacy and tolerability as second-line or subsequent treatments for patients with advanced non-small cell lung cancer (NSCLC). The objective response rate was 28.8%, with a median progression-free survival of 2.7 months and a median overall survival of 9.5 months.

What is known and what is new?

- The efficacy of second-line or later-line treatments for advanced NSCLC remains suboptimal. Both S-1 monotherapy and combination therapy have shown promising anti-tumor activity in patients at advanced stages of disease progression, with mild adverse effects.
- In our study, we first assessed the efficacy and safety of combining S-1 with other therapies in advanced NSCLC patients. In patients with late-stage NSCLC lacking driver gene mutations, compromised physical capacity, multiple comorbidities, and elevated Eastern Cooperative Oncology Group performance status scores, which have led to limited therapeutic alternatives, S-1 demonstrated potential as a viable option. Both S-1 monotherapy and combination therapy exhibited encouraging efficacy and were well-tolerated as second-line or subsequent-line interventions for advanced NSCLC patients.

What is the implication, and what should change now?

- Future research should focus on conducting large-scale, multicenter studies to further investigate the potential benefits of S-1 therapy. Additionally, new investigations could explore the efficacy of combining S-1 with immunotherapy. The role of S-1 as a therapeutic option for advanced NSCLC warrants further elucidation.

Methods

Patients

All patient-related procedures adhered to the principles outlined in the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Zhejiang Cancer Hospital (No. IRB-2023-615). Individual consent for this retrospective analysis was waived. A retrospective analysis was conducted on the medical records of patients diagnosed with advanced NSCLC at tumor-node-metastasis (TNM) classification stage IIIB/IV, who received S-1 as second-line or subsequent therapy at Zhejiang Cancer Hospital in Hangzhou, China, between January 2018 and August 2023. Enrollment criteria in this study were as follows: (I) patients with histologically or cytologically confirmed NSCLC; (II) Eastern Cooperative Oncology Group (ECOG) PS scores 0–2; (III) following first-line chemotherapy, the patient exhibited recurrent tumor growth and demonstrated resistance to the first-line therapeutic approach; (IV) patients with unresectable stage IIIB/IV NSCLC; and (V) patients not harboring epidermal growth factor receptors (EGFRs) mutation or anaplastic lymphoma kinases (ALKs) rearranged. Exclusion criteria in this study were as follows: (I) patients with other types of malignancy; and (II) patients lacking response evaluation due to insufficient follow-up of less than 4 weeks or loss to follow-up. Patients' data were collected including age, gender, histological subtype, clinical TNM stage (8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system) (14), smoking status, ECOG PS scores, liver metastases, brain metastases, pleural effusion, programmed cell death 1-ligand 1 (PD-L1) expression, date of treatment start, treatment regimens, lines of treatment regimens, best of efficacy, previous radiotherapy, previous surgical resection, date of disease progression, date of death, adverse events (AEs).

Treatments

Based on their treatment regimen, patients were categorized into groups receiving either S-1 monotherapy or S-1 combination therapy. S-1 were selected according to body surface area (BSA): BSA <1.25 m^2, 40 mg twice daily (b.i.d.); BSA ≥1.25 m^2, but <1.5 m^2, 50 mg b.i.d.; and BSA ≥1.5 m^2, 60 mg b.i.d. S-1 was administered orally at a daily dose in two divided doses after a meal for a duration of 4 weeks, followed by a drug-free interval of 2 weeks (one cycle). The chemotherapy regimens involved gemcitabine, which was administered at a dose of 1,250 mg/m^2 on days 1 and 8 every 3 weeks. ICIs involved camrelizumab, tislelizumab, sintilimab, nivolumab, toripalimab, sugemalimab. Camrelizumab, tislelizumab, sintilimab at a dose of 200 mg by intravenous (iv) infusion every 3 weeks. Nivolumab at a dose of 360 mg via iv infusion every 3 weeks. Toripalimab at a dose of 240 mg by iv infusion every 3 weeks. Sugemalimab at a dose of 1,200 mg by iv infusion every 3 weeks. Antiangiogenic drugs included bevacizumab, anlotinib, and endostar. Bevacizumab was administered at a dose of 15 mg/kg by iv infusion every 3 weeks. Anlotinib was administered at varying doses (12 mg/10 mg/8 mg) via iv infusion over 2 weeks, with a 1-week break, dependent on patient tolerance levels. Endostar was administered at a dose of 7.5 mg/m^2 by iv infusion daily for 2 weeks and stopped for 1 week.

Assessment of response and toxicity

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used to evaluate tumor responses (15). After starting the S-1 therapy, a routine evaluation was conducted every 6–8 weeks. OS was the primary endpoint, and it was measured from the date of the initial S-1 treatment to the date of death. The secondary endpoints were PFS, objective response rate (ORR), disease control rate (DCR), and AEs. PFS was defined as the period from the initiation of S-1 treatment to disease progression or death. ORR refers to the proportion of patients who had a complete response (CR) or partial response (PR), and the DCR refers to that of patients who had a CR or PR or stable disease (SD).

AEs were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 developed by the National Cancer Institute.

Statistical analysis

All statistical analyses were performed using GraphPad Prism software version 9.5 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS statistical software version 25.0 (IBM Corp., Armonk, NY, USA). Baseline characteristics were compared in the two groups using Chi-squared and Fisher's exact tests. OS and PFS were assessed using Kaplan-Meier survival curves, with differences between groups detected using log-rank tests. A multivariate logistic regression analysis was conducted to identify independent prognostic factors associated with OS, focusing on variables

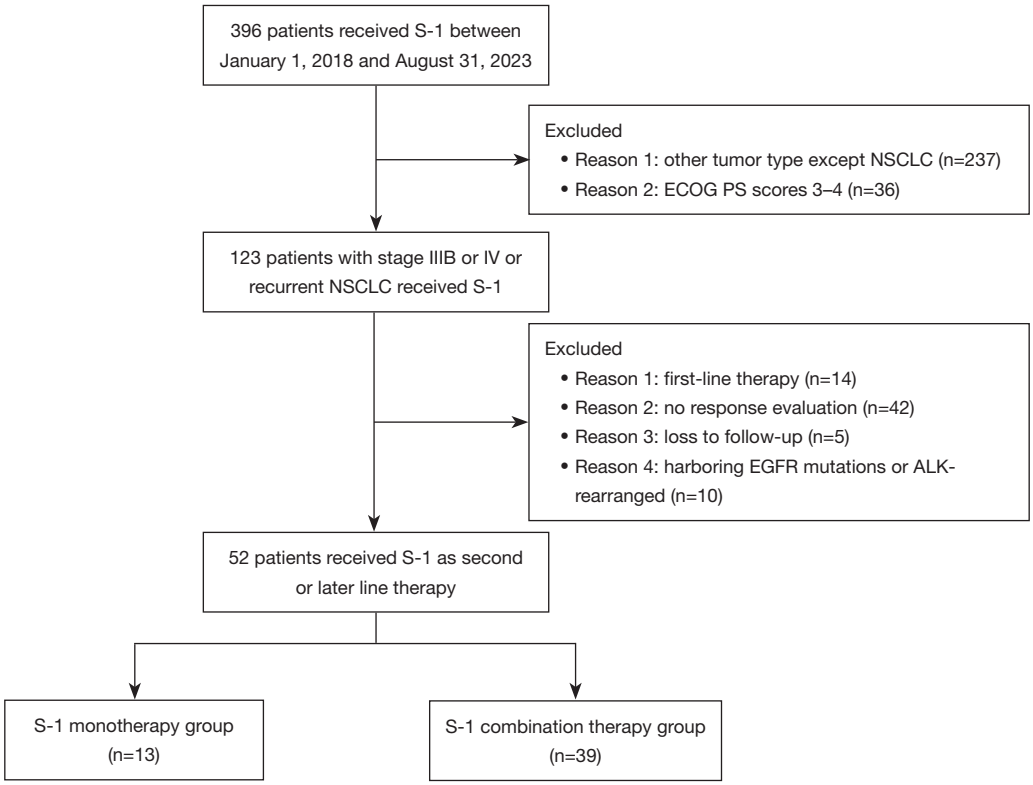


Figure 1 Flow chart of patients' treatment schedule. NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

with P values below 0.2 in the univariate regression analysis. Two-sided P values <0.05 were considered statistically significant.

Results

Patient characteristics

Between January 2018 and August 2023, 396 patients received S-1 in our cancer center. There were 237 patients excluded for other tumor types, and 36 patients were excluded for ECOG PS 3–4. There were 123 patients with stage IIIB, IV, or recurrent NSCLC treated with S-1. Fourteen patients who received S-1 as first-line therapy, 42 patients without response evaluation, and 10 patients with positive EGFR mutations or ALK rearranged were excluded from the study. The follow-up rate was 90.4%, and five patients were lost to follow-up (*Figure 1*).

As a result, a total of 52 patients who received S-1 as a second-line or later therapy were included in the analysis. The monotherapy group consisted of 13 patients, while the combination group consisted of 39 patients. A total of 75.0% of patients were in the combination group. One (1.9%) patient received S-1 plus chemotherapy, 28 (53.8%) patients received S-1 plus immunotherapy, 10 (19.2%) patients received S-1 plus antiangiogenic therapy. As shown in *Table 1*, most variables, except histologic features, were similar between the two groups at baseline. The rate of adenocarcinoma patients was 23.1% in the combination group and 53.8% in the monotherapy therapy group. Among the two groups, the mean age was 64 years, ranging from 58 to 70 years. A total of 35 (67.3%) patients exhibited a PS of 1, while 17 patients (32.7%) displayed a PS of 2. Nine (17.3%) patients were stage IIIB, while 43 (82.7%) patients were stage IV. Fourteen (26.9%) patients were never smokers. Thirty-six (69.2%) patients had squamous cell carcinoma on histopathology of their biopsy specimen, while 16 (30.7%) patients had adenocarcinoma. Twenty-five (48.1%) patients had received second-line therapy, and 27 (51.9%) patients had received third-line or later therapy. Eight (15.4%) patients had developed liver metastases and 4 (7.7%) patients had developed brain

Table 1 Baseline patient characteristics at the time of S-1 initiation (n=52)

Items	Total (n=52)	S-1 monotherapy (n=13)	S-1 combination therapy (n=39)	P value
Age (years)				0.86
Median [range]	64 [58, 70]	62 [58, 68]	64 [58, 70]	
≥70	13 (25.0)	3 (23.1)	10 (25.6)	
Sex				0.42
Male	47 (90.4)	11 (84.6)	36 (92.3)	
Female	5 (9.6)	2 (15.4)	3 (7.7)	
TNM stage				0.83
IIIB	9 (17.3)	3 (5.8)	6 (15.4)	
IV	43 (82.7)	10 (19.2)	33 (84.6)	
Smoking status				0.72
NA	14 (26.9)	4 (30.8)	10 (25.6)	
Current/former	38 (73.1)	9 (69.2)	29 (74.4)	
ECOG PS score				0.13
1	35 (67.3)	11 (84.6)	24 (61.5)	
2	17 (32.7)	2 (15.4)	15 (38.5)	
Histologic features				0.04
Squamous cell carcinoma	36 (69.2)	6 (46.2)	30 (76.9)	
Adenocarcinoma	16 (30.7)	7 (53.8)	9 (23.1)	
Liver metastases				>0.99
No	44 (84.6)	11 (84.6)	33 (84.6)	
Yes	8 (15.4)	2 (15.4)	6 (15.4)	
Brain metastases				0.23
No	48 (92.3)	13 (100.0)	35 (89.7)	
Yes	4 (7.7)	0 (0.0)	4 (10.3)	
Pleural effusion				0.87
No	35 (67.3)	9 (69.2)	33 (84.6)	
Yes	17 (32.7)	4 (30.8)	6 (15.4)	
PD-L1 expression				0.14
Negative/NA	46 (88.5)	13 (100.0)	33 (84.6)	
Positive	6 (11.5)	0 (0.0)	6 (15.4)	
Previous radiotherapy				0.82
No	45 (86.5)	11 (84.6)	34 (87.2)	
Yes	7 (13.5)	2 (15.4)	5 (12.8)	

Table 1 (*continued*)

Table 1 (*continued*)

Items	Total (n=52)	S-1 monotherapy (n=13)	S-1 combination therapy (n=39)	P value
Previous surgical resection				>0.99
No	40 (76.9)	10 (76.9)	30 (76.9)	
Yes	12 (23.1)	3 (23.1)	9 (23.1)	
Previous first-line chemoimmunotherapy regimen				–
Albumin paclitaxel + carboplatin/cisplatin/nedaplatin ± immunotherapy	22 (42.3)	–	–	
Pemetrexed + carboplatin/cisplatin/nedaplatin ± immunotherapy/bevacizumab	20 (38.5)	–	–	
Gemcitabine + carboplatin/cisplatin/nedaplatin ± immunotherapy	8 (15.4)	–	–	
Immunotherapy monotherapy	2 (3.8)	–	–	
Treatment regimen				–
S-1 monotherapy	13 (25.0)	–	–	
S-1 + chemotherapy	1 (1.9)	–	–	
S-1 + immunotherapy	28 (53.8)	–	–	
S-1 + antiangiogenic therapy	10 (19.2)	–	–	
Number of lines				0.23
Median [IQR]	3 [2, 4]	4 [2.5, 4]	2 [2, 3]	
Second-line therapy	25 (48.1)	3 (23.1)	22 (56.4)	
≥ Third-line treatment	27 (51.9)	10 (76.9)	17 (43.6)	

Data are presented as n (%). TNM, tumor-node-metastasis; NA, not available; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1; IQR, interquartile range.

metastases. A total of 17 (32.7%) patients had pleural effusion. Among the 52 patients, 6 (11.5%) patients had positive PD-L1 expression. Seven (13.5%) patients received previous radiotherapy, while 12 (23.1%) patients received previous surgical resection. Twenty-two (42.3%) patients received albumin paclitaxel + carboplatin/cisplatin/nedaplatin ± immunotherapy as previous first-line chemoimmunotherapy regimen, 20 (38.5%) patients received pemetrexed + carboplatin/cisplatin/nedaplatin ± immunotherapy/bevacizumab as previous first-line chemoimmunotherapy regimen, 8 (15.4%) patients received gemcitabine + carboplatin/cisplatin/nedaplatin ± immunotherapy as previous first-line chemoimmunotherapy regimen, while 2 (3.8%) patients received immunotherapy monotherapy as previous first-line regimen.

Efficacy

Among all 52 patients, the best response to S-1 treatment was PR in 15 patients (28.8%), SD in 20 patients (38.5%), and progressive disease (PD) in 17 patients (32.7%). The ORR was 28.8%, and the DCR was 67.3% (*Table 2*). A representative example was presented in *Figure 2*.

Survival analysis

The last follow-up date was August 31, 2023. After the follow-up period, 16 patients were still alive, while 36 had

Table 2 Tumor response in patients with advanced NSCLC receiving S-1 as second-line or later therapy

Items	Total (n=52), n (%)
PR	15 (28.8)
SD	20 (38.5)
PD	17 (32.7)
ORR	15 (28.8)
DCR	35 (67.3)

NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

passed away. The median follow-up time was 7.4 months (range, 4.8–14.6 months) for all patients and 6.3 months (range, 4.1–13.2 months) for living patients. The median PFS was 2.7 months [95% confidence interval (CI): 2.1–2.8], and the median OS was 9.5 months (95% CI: 6.3–12.6) for the total cohort.

In the subgroup analysis, the median PFS of patients who had received prior radiotherapy (5.5 months; 95% CI: 4.4–6.6) was significantly longer than patients who did not receive prior radiotherapy (2.5 months; 95% CI: 2.1–2.9) (P=0.047); median OS of patients who had received prior radiotherapy (21.0 months; 95% CI: 0–45.9) was significantly longer than patients who did not receive prior radiotherapy (9.5 months; 95% CI: 6.1–12.9) (P=0.01) (*Figure 3*).

We further analyzed the association between ECOG PS scores and long-term survival in the total cohort. The results showed that patients with ECOG PS score of 1 had better PFS (4.4 months; 95% CI: 2.3–6.6 *vs.* 1.7 months; 95% CI: 0.9–2.5; P<0.001) and OS (13.5 months; 95% CI: 8.4–18.7 *vs.* 8.0 months; 95% CI: 2.1–13.8; P=0.01) than patients with ECOG PS score of 2 (*Figure 4*).

Prognostic factors

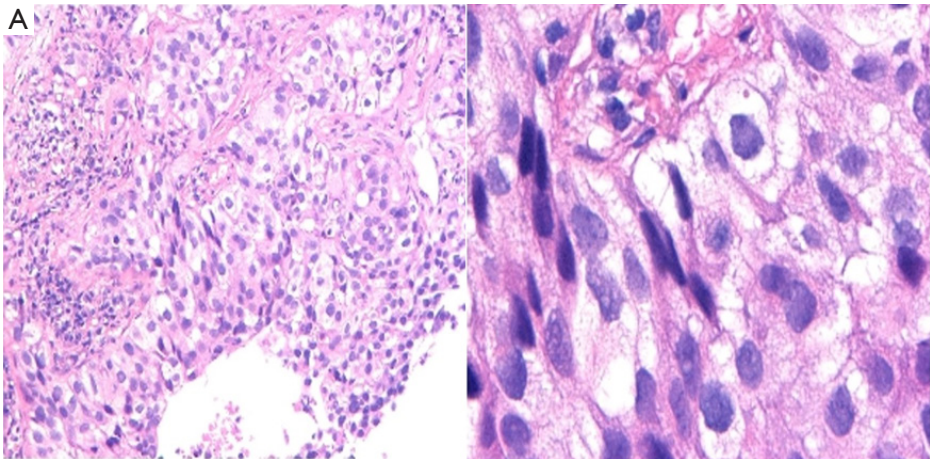
A multivariate analysis utilizing the logistic regression model was conducted to identify potential predictive factors of OS, as shown in *Table 3*. Additionally, univariate logistic regression analysis was performed to assess risk factors, with variables demonstrating a P value of less than 0.2 (ECOG PS scores, brain metastasis, pleural effusion, treatment regimen, number of lines) were included in multivariate regression analysis. S-1 combined therapy was associated with better OS than S-1 monotherapy [odds ratio (OR), 0.03; 95% CI: 0.00–0.64; P=0.03]. While the OS was significantly shorter for those who received S-1 as a later-line treatment than for those who received S-1 as a second-line treatment (OR, 7.61; 95% CI: 1.07–54.02; P=0.042).

Toxicities

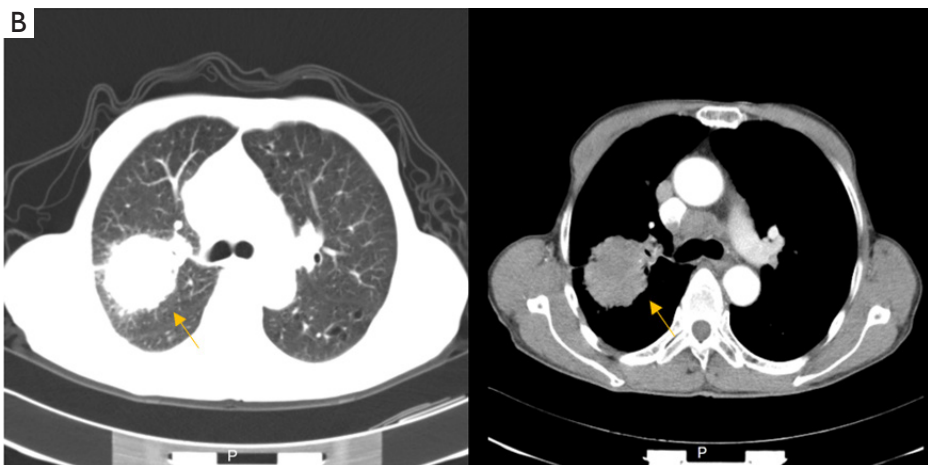
The incidence of AEs is shown in *Table 4*. Among the total cohort of patients, both the S-1 groups were well tolerated. The most common adverse reactions were anemia (12, 23.1%), platelet count decreased (5, 9.6%), elevated creatinine (5, 9.6%), pneumonitis (5, 9.6%), fatigue (4, 7.7%), elevated AST/ALT (4, 7.7%), white blood cell count decreased (2, 3.8%), neutrophil count decreased (2, 3.8%), dizziness (2, 3.8%), hypothyroidism (2, 3.8%), hand-foot syndrome (1, 1.9%), abdominal distension (1, 1.9%), elevated serum amylase (1, 1.9%). Most of the AEs were grade 1–2, only 3 (5.7%) patients showed grade 3–4 AEs (*Table 4*).

Discussion

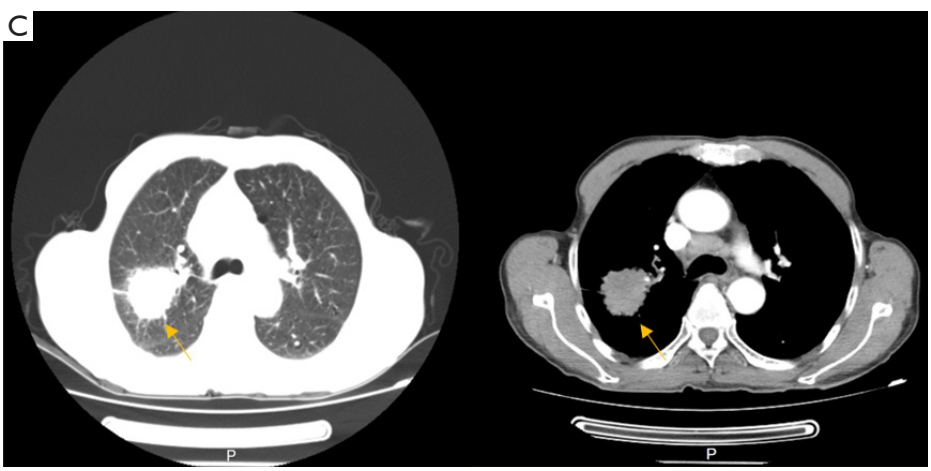
In the realm of advanced NSCLC patients who have experienced progression following platinum-based chemotherapy and ICI therapy, docetaxel monotherapy has emerged as the preferred treatment option. However, the effectiveness of docetaxel as second-line chemotherapy is not satisfactory. In a study conducted by Hanna *et al.*, patients with advanced NSCLC who had previously received chemotherapy were given docetaxel monotherapy (16). The ORR was found to be less than 10%, the median PFS was less than 3 months, and the median OS ranged from 6 to 8.3 months. Moreover, the toxicities associated with docetaxel monotherapy were notably severe. Additionally, not all patients were able to tolerate docetaxel, particularly those with ECOG PS scores ≥2. ICIs have emerged as the preferred treatment modality for disease progression following initial platinum-based chemotherapy. Various studies, including CheckMate-078 (17), KEYNOTE-010 (18), and OAK (19) have illustrated that single-agent immunotherapy can result in extended survival rates in the second-line setting when compared to docetaxel. Nevertheless, the utilization of immunotherapy monotherapy in second-line treatment has been constrained by the elevated expenses associated with immunotherapy agents and the escalating utilization of programmed death 1 (PD1)/PD-L1 inhibitors in first-line therapy. Anlotinib was approved by the National Medical Products Administration (NMPA) in China in 2008 as



HE-stained pathological images



Baseline



After S-1 monotherapy

Figure 2 Chronological summary of pathological images and pathological images of patient 1, a 78-year-old male. (A) Pathological diagnosis from transcutaneous needle biopsy of the right lung mass was adenocarcinoma (magnification, ×100 in the left and ×400 in the right). (B) At the baseline (August 2019), the CT scan showed a 4.1 cm × 4.8 cm right lung nodule (arrows). (C) Six weeks later, after two cycles of S-1 monotherapy (September 2019), the CT scan showed a 3.9 cm × 3.3 cm right lung nodule (arrows). HE, hematoxylin-eosin; CT, computed tomography.

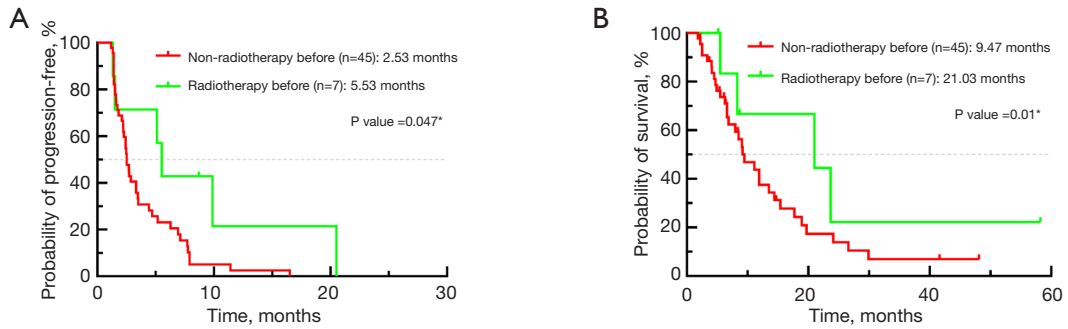


Figure 3 Survival analysis for patients with radiotherapy before or non-radiotherapy before. (A) Comparison of PFS for patients with radiotherapy before and those with non-radiotherapy before. The median PFS of patients with radiotherapy before was 5.5 months (95% CI: 4.4–6.6) and that of patients with non-radiotherapy before was 2.5 months (95% CI: 2.1–2.9) (P=0.047*). (B) Comparison of OS for patients with radiotherapy before and those with non-radiotherapy before. The median OS of patients with radiotherapy before was 21.0 months (95% CI: 0–45.9) and that of patients with non-radiotherapy before was 9.5 months (95% CI: 6.1–12.9) (P=0.01*). *, P<0.05. PFS, progression-free survival; CI, confidence interval; OS, overall survival.

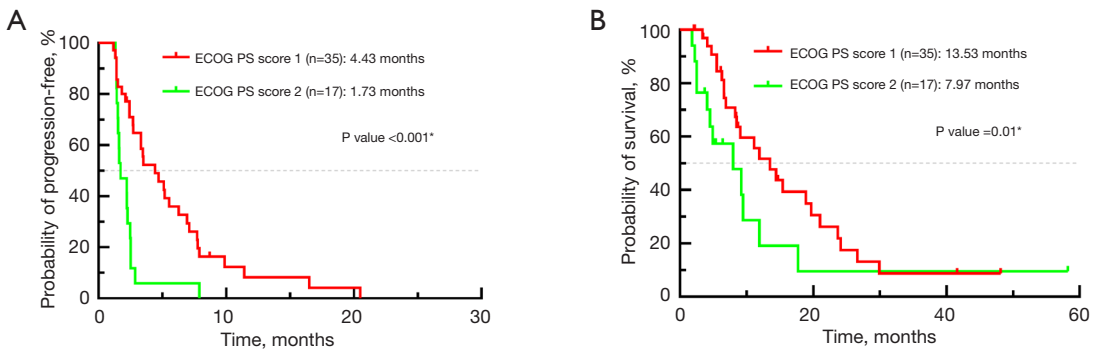


Figure 4 Survival analysis for patients with ECOG PS score 1 or ECOG PS score 2. (A) Comparison of PFS for patients with ECOG PS score 1 and those with ECOG PS score 2. The median PFS of patients with ECOG PS score 1 was 4.4 months (95% CI: 2.3–6.6) and that of patients with ECOG PS score 2 was 1.7 months (95% CI: 0.9–2.5) (P<0.001*). (B) Comparison of OS for patients with ECOG PS score 1 and those with ECOG PS score 2. The median OS of patients with ECOG PS score 1 was 13.5 months (95% CI: 8.4–18.7) and that of patients with ECOG PS score 2 was 8.0 months (95% CI: 2.1–13.8) (P=0.01*). *, P<0.05. ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; CI, confidence interval; OS, overall survival.

a third-line treatment for NSCLC (20). However, drug resistance eventually emerged, and the improvement in OS was finite.

In this study, we first assessed the efficacy and safety of combining S-1 with other therapies in advanced NSCLC patients. 25% of patients were in the monotherapy group, and 75.0% of patients were in the combination group. The ORR was 28.8% of the total population. Median PFS and OS were 2.7 and 9.5 months for the total cohort, respectively. The fluorouracil-based oral prodrug S-1 was approved in Japan in 2004 for the treatment of NSCLC. A meta-analysis conducted by Abdel-Rahman *et al.* demonstrated that S-1-based regimens are associated with favorable efficacy outcomes in NSCLC (21).

Of particular note, compared with patients who had not received prior radiotherapy, patients who had received prior radiotherapy exhibited superior OS and PFS curves. Analysis of the PACIFIC trial demonstrated that the concurrent administration of chemoradiotherapy and immunotherapy led to a significant improvement in OS, with a median OS of 47.5 months compared to 29.1 months [hazard ratio (HR), 0.72; 95% CI: 0.59 to 0.89] (22) and a

Table 3 Logistic regression analysis of survival status in NSCLC patients treated with S-1

Factors	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)				
<70	Ref.			
≥70	0.65 (0.02–20.07)	0.80		
Sex				
Male	Ref.			
Female	0.05 (0.00–45.00)	0.38		
Smoking status				
Never	Ref.			
Current/former	20.10 (0.13–3,223.61)	0.25		
ECOG PS scores				
1	Ref.			
2	37.05 (0.53–2,581.67)	0.10	3.93 (0.67–22.97)	0.13
Histologic features				
Squamous cell carcinoma	Ref.			
Adenocarcinoma	3.13 (0.14–71.10)	0.47		
Liver metastasis				
No	Ref.			
Yes	3.369 (0.09–132.77)	0.52		
Brain metastasis				
No	Ref.			
Yes	0.00 (0.00–0.84)	0.045	0.09 (0.00–2.24)	0.14
Pleural effusion				
No	Ref.			
Yes	22.57 (0.51–1,002.68)	0.11	3.33 (0.42–26.59)	0.26
PD-L1				
Negative/undone	Ref.			
Positive	2.49 (0.10–60.04)	0.58		
Previous surgical resection				
No	Ref.			
Yes	2.46 (0.02–322.99)	0.72		
Previous radiotherapy				
No	Ref.			
Yes	0.12 (0.00–19.99)	0.42		
Treatment regimen				
S-1 monotherapy	Ref.			
S-1 combined therapy	0.01 (0.00–1.284)	0.06	0.03 (0.00–0.64)	0.03*
Number of lines				
Second-line therapy	Ref.			
≥ Third-line treatment	186.77 (1.41–24,779.78)	0.04	7.61 (1.07–54.02)	0.042*

*, P<0.05. NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval; ref., reference; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death-ligand 1.

Table 4 Incidence of AEs

Treatment-related AEs	Any grade	Grade ≥3
Anemia	12 (23.1)	0 (0.0)
White blood cell count decreased	2 (3.8)	0 (0.0)
Neutrophil count decreased	2 (3.8)	2 (3.8)
Platelet count decreased	5 (9.6)	1 (1.9)
Pneumonitis	5 (9.6)	0 (0.0)
Nausea and/or vomiting	0 (0.0)	0 (0.0)
Hand-foot syndrome	1 (1.9)	0 (0.0)
Dizziness	2 (3.8)	0 (0.0)
Abdominal distension	1 (1.9)	0 (0.0)
Fatigue	4 (7.7)	0 (0.0)
Hypertension	0 (0.0)	0 (0.0)
Hypothyroidism	2 (3.8)	0 (0.0)
Elevated creatinine	5 (9.6)	0 (0.0)
Elevated AST/ALT	4 (7.7)	0 (0.0)
Elevated serum amylase	1 (1.9)	0 (0.0)

Data are presented as n (%). AE, adverse event; ALT, alanine aminotransferase; AST, aspartate transaminase.

median PFS of 16.9 months compared to 5.6 months (HR, 0.55; 95% CI: 0.45 to 0.68) between the immunotherapy group and placebo group. It may be that immunotherapy was used during radiotherapy for all patients who had received prior radiotherapy, of which the synergy between immunotherapy and radiotherapy enhanced therapeutic responses. Moreover, it was observed that patients with an ECOG PS of 1 exhibited enhanced PFS and OS in comparison to those with a PS of 2. The ECOG PS score serves as a comprehensive indicator of a patient's general health condition and is commonly utilized in guiding recommendations for antitumor therapies (23). A recent multicenter study conducted in Japan revealed a significant correlation between an ECOG PS score of ≥2 and a diminished OS outcome (24).

Additionally, results from multivariate logistic regression analysis indicated that the use of combination therapy involving S-1 independently predicted OS. This discovery aligned with the findings of the clinical trial (11,25,26), which demonstrated that combination therapy with S-1 significantly enhanced antitumor efficacy. However, the small sample size may limit the accuracy of the conclusions. A large multicenter sample are needed in future studies due to the possibility of bias in small sample sizes.

Utilizing multivariate logistic regression analysis, our research identified the treatment line as an independent adverse prognostic factor for OS. Specifically, individuals who received S-1 as a later-line therapy experienced a significantly decreased OS compared to those who received it as a second-line treatment. The later the treatment lines, and the worse the physical function, the poorer the prognosis, the initiation of the S-1 treatment regimen promptly is recommended to optimize outcomes.

In our cohort, the most common AE was anemia, which occurred in 23.1% of patients. Followed by platelet count decreased, elevated creatinine and pneumonitis, which occurred in 9.6% of patients. Most of the AEs were grade 1–2, only 5.7% of patients showed grade 3–4 AEs. In a clinical trial by Nishijima-Futami *et al.* (26), the addition of S-1 to bevacizumab did not increase toxicity. A meta-analysis also demonstrated that the S-1-based regimens showed milder AEs in high-grade nausea/vomiting, anorexia, leukopenia, neutropenia, and febrile neutropenia (all $P<0.05$) (27).

Of note, there are certain limitations in this study. First, the limited sample size in this study had implications for statistical power, potentially introducing selection and measurement biases. Due to the small sample size, conclusions may not be generalized to the entire population. Further multicenter large sample studies are needed in the future. Furthermore, the retrospective design of this study introduced inherent limitations associated with retrospective data collection, potentially impacting survival time and treatment response.

Conclusions

In conclusion, the study findings suggest that S-1 exhibits potential efficacy and tolerability with minimal toxicity as a second-line or subsequent treatment for advanced NSCLC, in comparison to standard treatment options such as docetaxel monotherapy or docetaxel plus ramucirumab, regardless of whether it is administered as monotherapy or in combination. Moreover, combined therapy with S-1 and treatment line emerged as two significant independent predictors of OS. Given the constraints of the small sample size, additional prospective investigations are warranted to explore the potential efficacy of this therapeutic approach.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-940/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-940/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Zhejiang Cancer Hospital, Zhejiang, China (No. IRB-2023-615) and individual consent for this retrospective analysis was waived.

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