Review Article

Advances in monotherapy and combination therapy of S-1 for patients with advanced non-small cell lung cancer: a narrative review

Feiyi Cao[1,2], Cuiping Gu[1], Wei Hong[1], Ying Jin[1,3]

[1]Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, China; [2]Department of Medical Oncology, Postgraduate training base Alliance of Wenzhou Medical University (Zhejiang Cancer Hospital), Hangzhou, China; [3]Zhejiang Key Laboratory of Radiation Oncology, Hangzhou, China

Contributions: (I) Conception and design: W Hong; (II) Administrative support: All authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: F Cao, C Gu; (V) Data analysis and interpretation: Y Jin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wei Hong, MD. Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, No. 1 Banshan Road, Gongshu District, Hangzhou 310022, China. Email: hongwei@zjcc.org.cn; Ying Jin, MD. Department of Medical Oncology, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, No. 1 Banshan Road, Gongshu District, Hangzhou 310022, China; Zhejiang Key Laboratory of Radiation Oncology, Hangzhou 310022, China. Email: jinying@zjcc.org.cn.

Background and Objective: Both domestically and worldwide, non-small cell lung cancer (NSCLC) remain the leading cause of cancer-related death. As a fluorouracil derivative, S-1 which shows good efficacy and with few adverse effects have been widely confirmed in many solid tumors that it can provide a glimmer of hope for advanced NSCLC patients. We performed a review to explore the results of previous clinical studies of S-1 monotherapy as well as combined therapy involving S-1 in patients with advanced NSCLC.

Methods: A literature search was conducted in Medline and PubMed databases using the keywords "S-1" AND "Advanced lung cancer" OR "Pharmacological mechanism".

Key Content and Findings: A number of phase II clinical studies have reported on the favorable efficacy and excellent safety profiles of S-1 monotherapy in first-line or in posterior-line treatment for advanced NSCLC. In regard to S-1 in combination with chemotherapy, a number of phase II/III clinical studies have found the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) of these regimens are similar to or better than immunological monotherapy with fewer adverse effects. In the case of S-1 combined with anti-vascular therapy, a number of phase II single-arm clinical studies have found that S-1 combined with bevacizumab, anlotinib and apatinib in advanced NSCLC, exhibits higher antitumor activity, less adverse effects for patients with advanced NSCLC. A phase II single-arm clinical study of gefitinib combined with S-1 had the ORR of 85.7% in the first-line treatment of advanced NSCLC. As for the combination of S-1 and immunotherapy, preliminary results of a phase II retrospective clinical trial demonstrated that the ORR was significantly better with S-1 sequential after immune checkpoint inhibitors (ICIs) than with S-1 alone.

Conclusions: The findings indicate promising effectiveness and minimal toxicity with S-1 monotherapy and S-1 containing combined therapy in patients with advanced NSCLC to provide a potential treatment option for advanced NSCLC.

Keywords: Chemotherapy; immune checkpoint inhibitors (ICIs); non-small cell lung cancer (NSCLC); S-1; platinum combination

Submitted Oct 31, 2023. Accepted for publication Feb 29, 2024. Published online Apr 09, 2024.
doi: 10.21037/tcr-23-2019
View this article at: https://dx.doi.org/10.21037/tcr-23-2019

Introduction

Lung cancer has been expected to cause 127,070 deaths in the United States in 2023, making it the leading cause of cancer-related death worldwide (1). It is estimated that 80% of lung cancer cases are non-small cell lung cancers (NSCLC). A platinum-based doublet chemotherapy regimen combined with a programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) inhibitor is the current standard first-line treatment for advanced lung cancer (2-6). However, not all patients can tolerate platinum-based doublet chemotherapy combined with PD-1/PD-L1 inhibitor regimens, such as patients with a performance status (PS) ≥2. In addition, subsequent therapy after first-line treatment is limited and with unsatisfactory efficacy (7,8). Therefore, it is necessary to explore efficient regimens with better tolerance.

Fluorinated pyrimidine formulation S-1 contains tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in molar ratios of 1:0.4:1 (9). In the blood, tegafur primarily generates 5-fluorouracil (5-FU). The levels of 5-FU in tumor tissues and plasma are increased by CDHP, a competitive inhibitor of dihydropyrimidine dehydrogenase. By inhibiting the phosphorylation of 5-FU in the gastrointestinal tract, oxonate reduces the gastrointestinal toxicity of 5-FU. The S-1 drug is approved for treating locally advanced or metastatic stomach cancer that cannot be surgically removed. Other solid tumors, including NSCLC, have also been shown to benefit from S-1 (10-16). S-1 was approved in Japan in 2004 for the treatment of non-small cell lung cancer. S-1 monotherapy or combination therapy has also shown good anti-tumor activity in advanced NSCLC as first-line, second-line, or later-line treatments (17-21). In late-stage NSCLC patients with no driver gene mutations, weakened physical functions (22), multiple underlying diseases, and high PS scores, which have resulted in limited treatment options, S-1 could fill the gap.

This review summarized and described the results of previous clinical studies involving S-1 monotherapy and S-1 containing combined therapy in advanced NSCLC. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2019/rc).

Methods

A literature search was conducted in Medline and PubMed databases using the keywords "S-1" AND "Advanced lung cancer" OR "Pharmacological mechanism". The secondary references cited in articles obtained from the Medline and PubMed search were also retrieved. Methodology of the search is summarized in the *Table 1*. In this study, 25 studies on the S-1 monotherapy as well as on the S-1 containing combined therapy were included by searching the databases of PubMed and Medline. S-1 monotherapy and S-1 containing combined therapy were concluded to exhibit promising effectiveness and minimal toxicity (*Tables 2-5*).

Monotherapy of S-1

S-1 monotherapy as front-line treatment in advanced NSCLC

Two phase II studies evaluated single-agent S-1 as a first-line treatment for advanced NSCLC (*Table 2*). During the study, 32 elderly patients (age >70 years) with advanced NSCLC without chemotherapy were enrolled (23). According to the results, the objective response rate (ORR) was 22.6% [95% confidence interval (CI), 11–38%]. A median progression-free survival (mPFS) of 5.5 months was observed (95% CI, 2.5–10.0). There was 12.4 months median overall survival (mOS) (95% CI, 8.7–27.9). It was reported that grade 3 and 4 thrombocytopenia, neutropenia, anemia, leukopenia, and febrile neutropenia occurred in 9.4%, 6.3%, 6.3%, 3.1%, and 3.1% of patients, respectively. There were also few severe gastrointestinal adverse events (AEs), such as grade 3 nausea, vomiting, and diarrhea, occurring to 9.4%, 6.3%, and 3.1% of the patients, respectively. In a multicenter phase II study conducted by Goto *et al.*, 40 elderly patients (age ≥75 years) with advanced NSCLC who had not previously received chemotherapy were enrolled (24). There was an ORR of 7.9% (95% CI, 0.0–16.4%). Among all patients, the mPFS was 4.4 months (95% CI, 4.2–8.5) and the mOS was 17 months (95% CI, 11.2–18.7). The mPFS and mOS of patients with adenocarcinoma were 4.2 and 21.2 months, while those for patients with squamous cell carcinoma were 4.5 and 15.6 months, respectively. There were no significant differences of the mPFS and mOS between different histological subtypes. Severe hematologic AEs were minimal, i.e., among the hematologic AEs, grade 3 or 4 events only occurred in two patients with neutropenia (5.0%). Among the non-hematologic AEs, the incidence rates of grade 3 or 4 hyponatremia, hypokalemia, and anorexia were observed in 2 (5.0%), 1 (2.5%), and 3 (7.5%) patients, respectively.

Table 1 Methodology of the search for the review

Items	Specification
Date of search	December 1st 2022 to March 31st 2023
Databases and other sources searched	Medline and PubMed databases
Search terms used	"S-1" AND "Advanced lung cancer" OR "Pharmacological mechanism"
Time frame	2015–2023
Inclusion criteria	Restricted to articles published in English; without predefined restriction as to the study type
Selection process	All articles were screened by two authors (F.C. and C.G.) independently, with any disagreements resolved by a third author (W.H.). Eligibility of studies was based on the assessment of title, abstract and full-text

Table 2 Monotherapy of S-1

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1	Phase 2	First-line	32	22.6	5.5	12.4	Japan	In elderly patients with previously untreated advanced NSCLC, S-1 appears to be well tolerated and demonstrates encouraging activity	Kasai *et al.*, 2016 (23)
S-1	Phase 2	First-line	40	7.9	4.4	17	Japan	In elderly patients with previously untreated advanced NSCLC, a 2-week S-1 monotherapy treatment, with a 1-week interval was well tolerated and demonstrated promising efficacy	Goto *et al.*, 2018 (24)
S-1	Phase 2	Second- or later-line	8	7.1	1.5	7.6	Japan	Alternate-day S-1 administration can be a safe treatment regimen for elderly patients with NSCLC	Masuda *et al.*, 2018 (25)
S-1	Phase 2	Second- or later-line	96	8.3	3.1	9.6	Japan	S-1 monotherapy is effective and feasible as a subsequent-line treatment in elderly patients who were previously treated for NSCLC	Imai *et al.*, 2020 (26)
S-1 versus DTX	Phase 3	Second- or later-line	577	8.3	2.9	12.8	Japan	S-1 is equally as efficacious as docetaxel and offers a treatment option for patients with previously treated advanced NSCLC	Nokihara *et al.*, 2017 (27)
			577	9.9	2.9	12.5			
S-1 versus DTX	Phase 3	Second- or later-line	361	ND	2.9	13.4	Japan	S-1 had similar efficacy to docetaxel in patients with previously treated advanced NSCLC	Sugawara *et al.*, 2019 (28)
			359	ND	3.0	12.6			

ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; DTX, docetaxel; ND, not described.

Table 3 S-1 in combination with chemotherapy

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1 + CDDP	Phase 2	First-line	55	19.6	5.7	15.1	China	Oral S-1 plus cisplatin is an effective and safe first-line regimen for patients with advanced NSCLC	Lai *et al.*, 2020 (29)
S-1 + CDDP *vs.* DTX + CDDP	Phase 3	First-line	301 *vs.* 297	26.9 *vs.* 31.3	4.9 *vs.* 5.2	16.1 *vs.* 17.1	Japan	Oral S-1 plus cisplatin is not inferior to docetaxel plus cisplatin and is better tolerated in patients with advanced NSCLC	Kubota *et al.*, 2015 (30)
S-1 + CBDCA	Phase 2	First-line	33	30.3	4.4	15.7	Japan	The oral S-1 plus carboplatin regimen seems to be a favorable treatment option	Kuyama *et al.*, 2017 (31)
S-1 + Gem	Phase 2	First-line	20	40	6.4	17.8	Japan	The combination of gemcitabine and S-1 may be a promising and feasible regimen in the first-line setting for elderly patients with advanced NSCLC	Kaira *et al.*, 2017 (32)
S-1 + PTX	Phase 2	First-line	17	47.1	4.5	35	Japan	S-1 and paclitaxel showed satisfactory efficacy with mild toxicities in elderly patients with advanced NSCLC	Yoshimura *et al.*, 2019 (33)
S-1 + DTX	Phase 1, 2	Second- or later-line	39	7.7	4.5	13.3	Japan	Docetaxel plus oral S-1 had a lower response rate than anticipated; however, the survival data were encouraging	Takayama *et al.*, 2019 (34)
S-1 + PTX	Phase 2	Second- or later-line	40	27.5	6.5	20.7	Japan	S-1 and PTX co-therapy dose and schedule showed satisfactory efficacy, with mild toxicities, in patients with previously treated advanced NSCLC	Chihara *et al.*, 2019 (35)

ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; CDDP, cisplatin; CBDCA, carboplatin; Gem, gemcitabine; PTX, paclitaxel; DTX, docetaxel.

Table 4 S-1 in combination with anti-angiogenic therapy and EGFR-TKI

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1 + CDDP + Bev followed by Bev	Phase 2	First-line	39	64.1	7.3	21.4	Japan	S-1 plus cisplatin in combination with bevacizumab met the primary endpoint in patients with advanced non-squamous NSCLC. The response rate was anticipated to be high with acceptable toxicities	Miyanaga *et al.*, 2019 (36)
S-1 + CDDP + Bev followed by Bev *vs.* MTA + CDDP + Bev followed by Bev	Phase 2	First-line	24 *vs.* 24	83.3 *vs.* 54.2	11.5 *vs.* 13.3	39.0 *vs.* 22.2	Japan	The combination regimen of SCB was identified as having a similar activity and tolerability to that of PCB in patients with advanced non-squamous NSCLC	Kaira *et al.*, 2019 (37)
DTX + Bev *vs.* S-1 + Bev	Phase 2	Second- or later-line	45	20	3.9	16	Japan	DB and SB produced modest PFS benefits in the second-line treatment of patients with advanced non-squamous NSCLC	Nishino *et al.*, 2015 (38)
S-1 + Bev	Phase 2	Second- or later-line	28	14.3	3.2	11.4	Japan	Although SB was well tolerated, this combination did not provide any additional benefit in terms of PFS for patients with non-squamous NSCLC after failure of platinum-based chemotherapy	Yamada *et al.*, 2016 (39)
S-1 + Bev	Phase 2	Second- or later-line	30	6.7	4.8	13.8	Japan	The addition of bevacizumab to S-1 was tolerable, but not beneficial for patients with previously treated non-squamous NSCLC	Nishijima-Futami *et al.*, 2017 (40)
S-1 + anlotinib *vs.* anlotinib	Phase 2	Second- or later-line	40 *vs.* 30	20 *vs.* 10	3.9 *vs.* 3	8.1 *vs.* 6.2	China	Advanced squamous NSCLC patients with higher PS scores still benefit from anlotinib and S-1 combination regimen, even after they failed second-line or later-line systemic treatment	Xie *et al.*, 2020 (41)
S-1 + anlotinib	Phase 2	Second- or later-line	29	37.9	5.8	16.7	China	The combination of anlotinib with S-1 in the third- or later-line treatment of stage IV NSCLC shows promising antitumor activity and manageable toxicity in patients with NSCLC	Xiang *et al.*, 2021 (42)

Table 4 (*continued*)

Table 4 (*continued*)

Regimen	Phase	No. of lines of therapy	No. of patients	ORR (%)	mPFS (months)	mOS (months)	Region	Conclusion	References
S-1 + apatinib	Phase 2	Second- or later-line	31	22.6	3.3	13.8	China	Combination of low-dose apatinib and S-1 could be an effective and tolerable choice for advanced NSCLC patients who are unable to benefit from standard treatment	Zhou *et al.*, 2019 (43)
S-1 + apatinib	Phase 2	Second- or later-line	13	ND	4.7	9.8	China	Apatinib plus S-1 for advanced solid tumor patients as palliative treatment have a certain efficacy and was relatively safe	Chen *et al.*, 2021 (44)
S-1 + CBDCA + gefitinib	Phase 2	First-line	35	85.7	17.6	Not reached	Japan	Combination chemotherapy with carboplatin, S-1, and gefitinib is efficacious and well tolerated as a first-line treatment in advanced NSCLC patients with activating EGFR mutations	Tamiya *et al.*, 2015 (45)
S-1 + erlotinib	Phase 2	Second- or later-line	10	10	ND	ND	Japan	The combination therapy of erlotinib plus S-1 was not feasible in the EGFR wild-type NSCLC at least and early stopped	Nakahara *et al.*, 2021 (46)

EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; NSCLC, non-small cell lung cancer; CDDP, cisplatin; Bev, bevacizumab; MTA, pemetrexed; DTX, docetaxel; CBDCA, carboplatin; EGFR, epidermal growth factor receptor; ND, not described; SCB, S-1 + cisplatin + bevacizumab; PCB, pemetrexed + cisplatin + bevacizumab; DB, docetaxel plus bevacizumab; SB, S-1 plus bevacizumab.

Table 5 S-1 in combination with immunotherapy

Items	S-1			DTX		
	S-1 immediately after Nivo	S-1 in any line after Nivo	S-1 without ICIs	DTX-based CT immediately after Nivo	DTX-based CT in any line after Nivo	DTX without ICIs
N	15	21	23	24	30	66
ORR (%)	30	20	17.6	27.8	27.3	16
mPFS (months)	3.88	3.06	2.63	5.98	4.67	2.87

Conclusion: subsequent cytotoxic chemotherapy, especially immediately after nivolumab, has better treatment efficacy than that of regimens without ICI pretreatment [Tamura *et al.*, 2019, Japan (47)]. Nivo, nivolumab; ICIs, immune checkpoint inhibitors; CT, chemotherapy; DTX, docetaxel; ORR, objective response rate; mPFS, median progression-free survival.

The age of the patient plays an important role in determining the right chemotherapy regimen for them. Due to their compromised organ systems and comorbid conditions, older patients are more likely to experience chemotherapy-related AEs than younger patients. For this reason, elderly patients should select drugs with low toxicity. The efficacy and excellent safety profiles of S-1 monotherapy make it a promising first-line treatment for

advanced NSCLC, particularly in elderly patients.

S-1 monotherapy as second- or later-line treatment in advanced NSCLC

Four trials were conducted to assess the effectiveness of S-1 monotherapy in patients with previously treated NSCLC (*Table 2*). In a phase II prospective trial, Masuda *et al.* enrolled eight senior patients (age 75 years or older) and administered S-1 monotherapy to them (25). An ORR of 7.1% was reported (95% CI, 2–17.3%). A median PFS of 1.5 months was observed (95% CI, 0.9–1.8), as well as a median OS of 7.6 months (95% CI, 3–17.1). There were no AEs of grade 3 or higher. According to a phase II study published by Imai, single-agent S-1 exhibited anticancer activity in 96 elderly patients (aged 75 years or older) with platinum-resistant advanced NSCLC (26). An ORR of 8.3% (95% CI: 2.8–13.8%) was obtained. Second-line therapy had a median PFS of 3.1 months (95% CI: 1.7–5.4) compared with third- or later-line therapy at 3.4 months (95% CI: 2.5–4.2). The median OS for the second-line therapy group was 9.6 months (95% CI: 5.3–14.4) while that of the third- or later-line therapy group was 11.0 months (95% CI: 6.8–14.2). Grade 3 hematological toxicities included anemia (3.1%) and decreased platelet count (2.1%). Grade 3/4 non-hematologic toxicity consisted of anorexia (9.4%), nausea (3.1%), mucositis oral (2.1%), fatigue (1%), diarrhea (1%). Two randomized phase III studies were conducted to examine the non-inferiority of S-1 monotherapy in comparison to the docetaxel regimen as a result of these encouraging results. A total of 1,154 treated NSCLC patients were enrolled and randomly assigned to each group in Nokihara's study (27). In the S-1 arm, the ORR was 8.3% and in the docetaxel arm, it was 9.9%. In the S-1 arm, median PFS was 2.86 months (95% CI: 2.73–3.12), while in the docetaxel arm it was 2.89 months (95% CI: 2.79–3.09), respectively [hazard ratio (HR) =1.03; 95% CI: 0.91–1.17]. In the S-1 arm, median OS was 12.75 months (95% CI: 11.53–14.00), while in the docetaxel arm, it was 12.52 months (95% CI: 11.14–14.36) (HR =0.945; 95% CI: 0.833–1.073). There was no difference in PFS and OS between oral S-1 and docetaxel regimen, indicating non-inferiority of S-1 to docetaxel. Grade 3–4 hematologic toxicity included neutropenia (5.4% *vs.* 47.7%), anemia (2.6% *vs.* 1.4%), leukocytopenia (1.2% *vs.* 29.1%), thrombocytopenia (1.2% *vs.* 0.2%) and febrile neutropenia (0.9% *vs.* 13.4%) in the S-1 arm and docetaxel arm. Grade 3–4 major gastrointestinal toxicity included decreased appetite (6.5% *vs.* 2.7%), diarrhea (6.3% *vs.* 1.1%) in the S-1 arm and docetaxel arm. Sugawara enrolled 720 patients with treated NSCLC and randomly assigned them to each group in his study (28). In the S-1 group, median PFS was 2.9 months (95% CI: 2.8–3.9) and in the docetaxel group, median PFS was 3.0 months (95% CI: 2.8–3.6) (HR =1.04; 95% CI: 0.89–1.22). In the S-1 group, median OS was 13.4 months (95% CI: 12.1–15.2) and in the docetaxel group, median OS was 12.6 months (95% CI: 11–15) (HR =0.92; 95% CI: 0.79–1.08). PFS and OS for oral S-1 were not different from the docetaxel regimen. Grade ≥3 hematologic toxicity included neutropenia (6.7% *vs.* 54%), anemia (2.8% *vs.* 1.1%), thrombocytopenia (1.7% *vs.* 0%) in the S-1 arm and docetaxel arm. Grade ≥3 nonhematologic toxicity included stomatitis (3.4% *vs.* 1.1%), nausea (1.4% *vs.* 1.7%), vomiting (2% *vs.* 0.9%), decreased appetite (9.8% *vs.* 3.4%), diarrhea (8.4% *vs.* 0.9%), constipation (0.8% *vs.* 0.3%) and maculopapular rash (1.4% *vs.* 0.3%) in the S-1 arm and docetaxel arm.

In conclusion, a comparison of S-1 monotherapy to second-line and later-line treatments found similar response rates and better tolerability for patients with advanced or recurrent NSCLC who had previously received platinum-based therapy.

S-1 in combination with chemotherapy

S-1 combined with chemotherapy as front-line treatment in advanced NSCLC

Based on S-1's effectiveness as a single drug in NSCLC and 5-FU plus cisplatin's synergistic anticancer effects, 55 previously untreated patients with advanced NSCLC were treated with S-1 plus cisplatin in a phase II trial (*Table 3*) (29). The ORR was 19.6%. There were 5.7 months (95% CI: 3.3–8.4) of mPFS and 15.1 months (95% CI: 11.5–25.6) of mOS, respectively. A total of 11 patients (20%) experienced treatment-related AEs of grade 3 or above. Grade 3/4 hematological AEs included decreased neutropenia/neutrophil count in 3 patients (5.5%), platelet count in 1 patient (1.8%), and white blood cell count (WBC) in 1 patient (1.8%). Most commonly, diarrhea (7.3%) and neutropenia (3.6%) were reported as grade 3 non-hematological AEs. To compare the noninferiority of S-1 plus cisplatin with docetaxel plus cisplatin in patients with stage IIIB or IV NSCLC who had not previously received treatment, Kubota *et al.* conducted

the TCOG0701CATS study, a randomized phase III trial (30). There were 608 patients enrolled and assigned randomly to each group. In the cisplatin-S-1 arm, median PFS was 4.9 months, whereas in the cisplatin-docetaxel arm, it was 5.2 months (HR =1.113; 95% CI: 0.945–1.311). In the cisplatin-S-1 arm, median OS was 16.1 months, whereas in the cisplatin–docetaxel arm, it was 17.1 months (HR =1.013; 96.4% CI: 0.837–1.227). PFS and OS for oral S-1 plus cisplatin were not different from docetaxel plus cisplatin. Grade ≥3 hematologic toxicity included, neutropenia (22.9% *vs.* 73.4%, P<0.001), leukopenia (8.0% *vs.* 55.2%, P<0.001), anemia (13.6% *vs.* 17.8%, P=0.178), thrombocytopenia (5.6% *vs.* 1.3%, P=0.006) in the carboplatin-S-1 arm and carboplatin-paclitaxel arm. Grade ≥3 nonhematologic toxicity included anorexia (17.6% *vs.* 27.3%, P=0.001), nausea (9.6% *vs.* 19.9%, P<0.001), diarrhea (6% *vs.* 3.7%, P=0.930), vomiting (4% *vs.* 8.1%, P<0.001) and febrile neutropenia (3% *vs.* 7.4%, P<0.001) between the cisplatin-S-1 arm and in the cisplatin-docetaxel arm. A combination of carboplatin and S-1 was investigated as first-line therapy in 33 older patients with advanced NSCLC (aged 70 years or more) who had previously not been treated (31). The ORR was 30.3% (95% CI, 14.6–46%). The mPFS was 134 days (95% CI: 79–173). mOS was 479 days (95% CI: 250–571). Thrombocytopenia (42.4%), neutropenia (33.3%), and anemia (27.3%) were the most common grade 3 or higher hematological AEs. Grade 3 or 4 nonhematologic toxicity included febrile neutropenia (12.1%) and pneumothorax (3.03%) and erythema multiforme (3.03%). Even for older NSCLC patients (aged 70 years or more), the carboplatin + S-1 regimen proved viable and tolerated because of its excellent survival result and moderate toxicities. In chemotherapy-naive NSCLC patients, the combination of S-1 with cisplatin or carboplatin resulted in similar effectiveness results and reduced toxicity than those platinum-based doublet chemotherapy regimens.

According to a recent meta-analysis, these newer non-platinum regimens are effective for the treatment of advanced NSCLC due to their demonstrated activity and tolerable side effects (17). A combination of S-1 and other active agents with different mechanisms of action is being studied in order to achieve greater clinical benefits. Gemcitabine is a deoxycytidine analog with high anti-tumor activity and a favorable toxicity profile. A notable synergistic cytotoxic impact of Gemcitabine and 5-FU is seen, and it is sequence-dependent (18). Kaira *et al.* conducted a phase II study of gemcitabine combined with S-1 in 20 untreated elderly advanced NSCLC patients who were older than 70 years of age (32). The ORR was 40% (95% CI, 18.5–61.5%). In terms of PFS and OS, the median was 6.4 months (95% CI, 4.0–17.0) and 17.8 months (95% CI, 6.0–46.0). Neutropenia (25%), leukocytopenia (30%), anemia (0%), and thrombocytopenia (0%) were the hematological AEs reaching grades 3–4. The only non-hematological AE was a grade 3 skin rash, which occurred in 10% of cases. Paclitaxel is a taxane drug with favorable efficacy and safety as monotherapy for elderly patients (aged of ≥70 years) with advanced NSCLC. Yoshimura *et al.* conducted a phase II study, 17 untreated elderly patients (age of ≥70 years) received paclitaxel (PTX) plus S-1 (33). There was a 47.1% ORR, a PFS of 4.5 months (95% CI, 1.6–6.8) and an OS of 35 months (95% CI, 9.1– not reached), respectively. As for hematological AEs, there were 58.9% of leukopenia, 52.9% of neutropenia and 11.8% of anemia reaching grade 3 or more, respectively. Non-hematological toxicities reaching grade 3 or more were stomatitis (23.5%), febrile neutropenia (12%), pneumonitis (12%), diarrhea (6%), diarrhea (5.9%).

Combination regimens based on S-1 are similar to or better than platinum-based regimens in terms of ORR, PFS, and OS. As far as toxicity is concerned, S-1-based combinations are also superior to platinum-based combinations.

S-1 combined with chemotherapy in second-line or later line treatment for advanced NSCLC

Single agent chemotherapy is the standard second-line therapy for individuals with advanced NSCLC after first-line immunotherapy combined with chemotherapy. However, by the efficacy of second-line therapy's continued unsatisfactory performance and the patients' dismal prognosis, researches for new chemotherapeutic drugs and combination regimens as second-line treatment for advanced NSCLC were prompted. A study was performed by Takayama *et al.* to explore the efficacy of S-1 plus docetaxel against 39 previously treated NSCLC patients (*Table 3*) (34). The ORR was 7.7% (95% CI, 1.6–20.9%). The median PFS and mOS were 18.0 weeks (95% CI, 11.3–22.9) and 53.0 weeks (95% CI, 40.9–134.6), respectively. Leukocytopenia, neutropenia of grade 3 to 4 hematological toxicities were observed in 17 (43.6%) and 26 (66.7%). The most common non-hematologic toxicity was loss of appetite (7.7%), fever (5.1%), and interstitial pneumonia (5.1%). An evaluation of S-1 and PTX combined therapy in 40 patients

with advanced NSCLC following second-line treatment failure was conducted by Chihara *et al.* in a phase II clinical trial (*Table 3*) (35). The ORR was 27.5%. There were 6.5 months (95% CI, 3.2–8.5) and 20.7 months (95% CI, 8.1–25.0) of mPFS and mOS, respectively. Anemia (13%), neutropenia (48%), and thrombocytopenia (3%) were the most common hematologic toxicity grades 3 or 4. Non-hematologic toxicity grade 3/4 is composed of pneumonitis (10%), febrile neutropenia (8%), diarrhea (8%), and mucositis (5%).

A recent meta-analysis found that combination chemotherapy is more harmful than single-agent chemotherapy in the second-line setting (48). Even though monotherapy is currently recommended for recurrent NSCLC, combination chemotherapy for S-1 can easily be repeated for a longer period than monotherapy, likely equal to or longer than what is currently recommended. For patients who prefer outpatient or oral pharmaceutical treatment, S-1 may be an alternative option.

S-1 in combination with anti-angiogenic therapy

S-1 combined with bevacizumab as front-line treatment in advanced NSCLC

Humanized monoclonal antibody, Bevacizumab, targets vascular endothelial growth factors. A meta-analysis found that Bevacizumab significantly improved PFS and OS in patients with advanced NSCLC when combined with platinum-based chemotherapy (49). Additionally, two preclinical studies indicate that bevacizumab combined with 5-FU derivatives enhanced antitumor activity (50,51). In two phase II studies, platinum, S-1, and Bevacizumab combination chemotherapy was used as first-line therapy in patients with advanced NSCLC who had not previously received treatment (*Table 4*). In a phase II trial, 39 untreated NSCLC patients received oral S-1 plus Cisplatin and Bevacizumab (36). The ORR was 64.1% (95% CI, 47.2–78.8%). There were 7.3 months (95% CI, 5.9–8.7 months) of mPFS and 21.4 months (95% CI, 14.7– not reached) of mOS. Leukopenia (12.8%) and neutropenia (23%) were the two most common Grade 3 or 4 hematological AEs. As regards the most common non-hematological AEs (grade 3 or above), hypertension accounted for 28.2%, and pulmonary infection for 7.8%. Based on these encouraging results, an exploratory randomized phase II study was conducted to test if cisplatin + S-1 + bevacizumab (SCB) is non-inferior to cisplatin + pemetrexed + bevacizumab (PCB) (37). Forty-eight untreated patients were enrolled and randomly assigned to each group. PCB and SCB had ORRs of 54.2% and 83.3%, respectively (P=0.06). In both PCB and SCB administrations, the median PFS was 406 and 351 days, respectively (P=0.96), whereas the median OS was 678 and 1190 days (P=0.23). The results demonstrated that SCB regimen was non-inferior to carboplatin–paclitaxel arm concerning the ORR, OS, and PFS. Grade 3 or 4 toxicity included neutropenia (12.5% *vs.* 12.5%), anorexia (1.1% *vs.* 7.2%), infection (0.4% *vs.* 2.9%), skin rash (4.1% *vs.* 8.3%), hypertension (12.5% *vs.* 4.1%), urinary protein (8.3% *vs.* 4.1%) between the PCB regimen and SCB regimen. In individuals with untreated advanced NSCLC, bevacizumab combined with S-1 and platinum resulted in significant improvements in ORR, PFS, and OS compared with S-1 and cisplatin alone. It is possible to combine bevacizumab with platinum regimens as a first-line therapy for advanced NSCLC.

S-1 combined with anti-angiogenic therapy in second-line or later line treatment for advanced NSCLC

For the first time, Herbst *et al.* showed in 2007 that bevacizumab added to single-agent chemotherapy tended to increase PFS in the second-line situation (52). Three studies of S-1 plus bevacizumab have been conducted against previously treated NSCLC patients (*Table 4*). During a randomized phase II study, S-1 plus bevacizumab (SB) versus docetaxel plus bevacizumab (DB) were compared for non-inferiority (38). Each group received 45 patients who had previously received platinum-based chemotherapy through random assignment. There was a significant difference in ORR between the DB and SB arms (20.0% *vs.* 2.2%; P=0.015). In the DB arm, median PFS was 3.9 months (95% CI, 3.0–6.5) and in the SB arm, 3.5 months (95% CI, 2.9–5.9) (P=0.451). In the DB arm, median OS was 16.0 months (95% CI, 3.0–21.8) and in the SB arm, 21.7 months (95% CI, 11.6–31.5), respectively (P=0.406). There was noninferior to the DB arm with the SB arm concerning the PFS and OS. Grade 3 or 4 hematological toxicity included neutropenia (93.3% *vs.* 4.4%), anemia (2.2% *vs.* 0%), and febrile neutropenia (33.3% *vs.* 0%). Grade 3 or 4 non-hematological toxicity included infection (6.7% *vs.* 8.9%), fatigue (0% *vs.* 8.9%), hyponatremia (4.4% *vs.* 8.9%), proteinuria (2.2% *vs.* 6.7%), nausea (0% *vs.* 4.4%), mucositis oral (4.4% *vs.* 4.4%), diarrhea (0% *vs.* 4.4%), vomiting (0% *vs.* 2.2%), constipation (0% *vs.*

2.2%), increased alanine aminotransferase (ALT) (0% *vs.* 2.2%), increased aspartate aminotransferase (AST) (2.2% *vs.* 0%), bilirubin increased (0% *vs.* 2.2%), hyperkalemia (0% *vs.* 2.2%). With advanced non-squamous NSCLC, Yamada conducted a multicenter phase II study combining S-1 and Bevacizumab (39). Among the 28 treated NSCLC patients enrolled in the study, 14.3% had an ORR (95% CI, 1.3–27.3%). There were 3.2 months of median PFS (95% CI, 2.2–4.0) and 11.4 months of median mOS (95% CI, 8.9–13.9). There were 14.3% neutropenia, 3.6% leukopenia, 3.6% anemia, and 3.6% thrombocytopenia of grade 3 or 4 hematologic toxicity. Nonhematologic toxicity grade 3/4 included anorexia (10.7%), nausea (3.6%), stomatitis (3.6%), and diarrhea (3.6%). A multi-center phase II study was conducted by Nishijima-Futami *et al.* to assess the safety and effectiveness of S-1 + bevacizumab in 30 patients with recurrent non-squamous NSCLC (40). The ORR was 6.7% (95% CI, 1.8–21.3%). There was a median PFS of 4.8 months (95% CI, 2.7–6.4) and a median OS of 13.8 months (95% CI, 8.4– not available). Anemia (3.3%) was the only grade 3 hematologic toxicity. The most common grade 3 non-hematologic toxicities were diarrhea (10%), anorexia (10%), and infection (10%). No deaths or severe toxicity were associated with treatment.

The oral tyrosine kinase inhibitor anlotinib inhibits tumor growth and angiogenesis. Two studies of S-1 plus anlotinib have been performed against previously treated NSCLC patients (*Table 4*). An evaluation of S-1 plus anlotinib in 70 Chinese patients with EGFR mutation-negative advanced squamous cell lung cancer (SqCLC) with poor performance status (PS, 2–3) following progression of second- or later-line chemotherapy was conducted by Xie *et al.* (41). In terms of the short-term efficacy, there were no significant differences in ORR (20.0% *vs.* 10.0%, P=0.464) between the anlotinib+S1 group and the anlotinib group. As for the long-term efficacy, there was no significant difference in PFS between the anlotinib + S1 group and anlotinib group (3.87±0.29 *vs.* 3.00±0.24 months, P=0.11). mOS of patients in the anlotinib + S-1 group was longer than anlotinib group (8.07±0.56 *vs.* 6.17±0.42 months, P=0.022). No AE of grade 3 or higher requiring discontinuation was observed. In a phase II study, Xiang *et al.* evaluated S-1 plus anlotinib in 29 previously treated advanced NSCLC patients (42). There was an ORR of 37.9% (95% CI: 20.7–57.7%). A median PFS of 5.8 months (95% CI: 2.9–8.7) and a median mOS of 16.7 months (95% CI: 14.9–18.6) were obtained. Grade 3 AEs were consisted of nausea (11%), fatigue (7%), hypertension (7%), rash (7%) and hemorrhage (3%). Anlotinib and S-1 are both given orally without the requirement for an infusion pump or hospital stay, which may increase patient compliance and save expenses.

Inhibiting proliferation, migration, and neovascularization of endothelial cells, apatinib was a novel tyrosine kinase inhibitor (TKI) targeting VEGFR-2. The efficacy of apatinib for patients with advanced NSCLC who had failed second-line treatment has been demonstrated in a previous study. There have been two studies performed on NSCLC patients who had previously been treated with S-1 plus apatinib (*Table 4*). The combination of apatinib and S-1 was studied in 31 advanced NSCLC patients by Zhou in a retrospective study (43). There was an ORR of 22.6% (95% CI: 11.1–38.2%). There was 102 days mPFS (95% CI: 57–147) and 422 days mOS (95% CI: 148–696) during the study period. Treatment-related grade III toxicity were myelosuppression (10%), hand-foot-skin reaction (6%), hypertension (3%), fatigue (3%). In a phase II study conducted by Chen, 13 patients with treated advanced NSCLC were enrolled in the study to evaluate S-1 plus apatinib's efficacy and toxicity (44). The mOS was 9.8 months and the mPFS was 4.7 months. Grade 3 or above AEs were consisted of thrombocytopenia (12.1%), anemia (6.1%), leucopenia (6.1%), hypertension (15.2%), proteinuria (9.1%), hemorrhagic tendency (6.1%), hand-foot syndrome (3.0%) and diarrhea (3%).

S-1 in combination with EGFR-TKI

An epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) is the preferred treatment for patients with advanced NSCLC with the EGFR mutation. To compare the efficacy and safety of S-1 monotherapy and S-1 containing combined chemotherapy for NSCLC, a population-based observational study was conducted. As a result of the clinical trial, it was confirmed that S-1 chemotherapy is effective and tolerable against wild and mutated types of EGFR NSCLC (53). In NSCLC patients regardless of their EGFR mutation status, the combination of S-1 and gefitinib has a synergistic antiproliferative effect and is well tolerated (54). A total of 35 patients with untreated EGFR mutations received oral S-1 plus carboplatin and gefitinib (*Table 4*) (45). There was an ORR of 85.7%. All patients had a median PFS of 17.6 months [95% CI: 15.5– not described (ND)]. The mOS was not reached (95% CI: 27.9–ND). Neutropenia (17.1%), thrombocytopenia (14.3%), and anemia (5.7%) were among the hematologic toxicity grades 3 or 4. In grades 3 nonhematologic toxicity, elevated aminotransferase was

20.0%, diarrhea was 14.3%, febrile neutropenia was 2.9%, anorexia was 2.9%, and nausea was 2.9%. According to the findings, triplet chemotherapy using carboplatin, S-1, and gefitinib is an effective first-line treatment option for advanced NSCLC.

Erlotinib showed a positive survival benefit in previously treated advanced NSCLC, regardless of EGFR mutation status. Nakahara *et al.* conducted a phase I/II study of erlotinib combined with S-1 in treated advanced NSCLC (*Table 4*) (46). Phase II enrollment included 10 patients with PS 0, 1, or 2 EGFR-wild type NSCLC. The ORR in phase II was 10.0%, and the disease control rate (DCR) was 40.0%. On the basis of two treatment-related deaths, enrolment was halted after the enrollment of 10 participants. A combination of erlotinib and S-1 failed to work in patients with EGFR wild-type NSCLC and was stopped early.

S-1 in combination with immunotherapy

Immune checkpoint inhibitors (ICIs) and molecular target drugs have revolutionized lung cancer treatment over the past decade. Due to their significant benefit in treating metastatic disease and recurrent lung cancer without causing oncogene alterations, ICIs are now employed as first- and second-line treatments. A retrospective analysis of immunotherapy combined with S-1 in patients with advanced NSCLC was carried out by Tamura *et al.* (*Table 5*) (47). The outcomes were compared between patients with advanced NSCLC who received docetaxel-based chemotherapy or S-1 following nivolumab and those who received S-1 or docetaxel but not ICIs. S-1 without ICIs had an ORR of 17.6%, S-1 immediately after nivolumab had an ORR of 30.0% (OR =2.0, P=0.46), and in any lines after nivolumab had an ORR of 20.0% (OR =1.17, P=0.86). While docetaxel without ICIs had an ORR of 16.0%, docetaxel-based chemotherapy immediately after nivolumab had an ORR of 27.8% (OR =2.02, P=0.28), and in any lines after nivolumab had an ORR of 27.3% (OR =1.97, P=0.27). The median PFS to S-1 without ICIs was 2.63 months, S-1 immediately after nivolumab was 3.88 months (HR =1.00, P>0.99), and in any lines after nivolumab was 3.06 months (HR =0.81, P=0.60), respectively. While the median PFS for docetaxel without ICIs was 2.87 months, docetaxel-based chemotherapy immediately after nivolumab was 5.98 months (HR =0.69, P=0.23), and in any lines after nivolumab was 4.67 months (HR =0.76, P=0.34), respectively. The results showed that compared with regimens without ICI pretreatment, cytotoxic chemotherapy followed by nivolumab was more effective at treating advanced NSCLC. It is urgent to investigate the efficacy of S-1 in the treatment of NSCLC with ICIs.

Conclusions

S-1 is a novel oral anticancer agent that combines potassium oxonate, tegafur, and CDHP. The findings indicate a promising effectiveness and minimal toxicity with S-1 as monotherapy or in combinations with chemotherapy, anti-angiogenic therapy, targeted treatment and immunotherapy for patients with solid tumors as well as advanced NSCLC. In patients with advanced NSCLC with no driver gene mutation, age-related functional decline, multiple underlying diseases, and poor treatment tolerance have resulted in limited treatment options. S-1 has good clinical efficacy and a low incidence of adverse reactions, not only prolonging life but also improving the quality of life for patients, making it a new choice.

New researches have explored the S-1 in more detail. A preliminary clinical study conducted by Tanaka *et al.* explored the efficacy of combination of immunotherapy with S-1 and radiotherapy (55). This study of durvalumab after cisplatin plus S-1 (SP)-based chemoradiotherapy (CRT) found a 1-year PFS of 73%. A phase II clinical study conducted by Yamamoto *et al.* explored the frequency of S-1 administration. They found that both alternate-day and daily oral administrations of S-1 were demonstrated to be feasible in elderly patients with NSCLC (56). S-1's role as a therapeutic approach to advanced NSCLC will be further defined by results of ongoing and future trials.

Acknowledgments

Funding: This work was supported by the Medicine and Health Science and Technology Projects of Zhejiang Province (Grant number: No. 2023KY069).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2019/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2019/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2019/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.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48.
2. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. N Engl J Med 2020;383:1328-39.
3. Zhou C, Chen G, Huang Y, et al. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicentre, phase 3 trial. Lancet Respir Med 2021;9:305-14.
4. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
5. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
6. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
7. Leighl NB, Shepherd FA, Kwong R, et al. Economic analysis of the TAX 317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small-cell lung cancer. J Clin Oncol 2002;20:1344-52.
8. Hanna NH. Second-line chemotherapy for non-small-cell lung cancer: recent data with pemetrexed. Clin Lung Cancer 2004;5 Suppl 2:S75-9.
9. Shirasaka T, Shimamato Y, Ohshimo H, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996;7:548-57.
10. Yamada Y, Boku N, Mizusawa J, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4:501-10.
11. Kim HS, Ryu MH, Zang DY, et al. Phase II study of oxaliplatin, irinotecan and S-1 therapy in patients with advanced gastric cancer: the Korean Cancer Study Group ST14-11. Gastric Cancer 2018;21:802-10.
12. Mukai H, Uemura Y, Akabane H, et al. Anthracycline-containing regimens or taxane versus S-1 as first-line chemotherapy for metastatic breast cancer. Br J Cancer 2021;125:1217-25.
13. Ohba A, Ueno H, Shiba S, et al. Safety and efficacy of S-IROX (S-1, irinotecan and oxaliplatin combination therapy) in patients with advanced pancreatic cancer: A multicenter phase 1b dose-escalation and dose-expansion clinical trial. Eur J Cancer 2022;174:40-7.
14. Morizane C, Okusaka T, Mizusawa J, et al. Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: the FUGA-BT (JCOG1113) randomized phase III clinical trial. Ann Oncol 2019;30:1950-8.
15. Scanlon KJ, Newman EM, Lu Y, et al. Biochemical basis for cisplatin and 5-fluorouracil synergism in human ovarian carcinoma cells. Proc Natl Acad Sci U S A 1986;83:8923-5.
16. Araki H, Fukushima M, Kamiyama Y, et al. Effect of consecutive lower-dose cisplatin in enhancement of 5-fluorouracil cytotoxicity in experimental tumor cells in vivo. Cancer Lett 2000;160:185-91.
17. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 2005;23:2926-36.
18. Rauchwerger DR, Firby PS, Hedley DW, et al. Equilibrative-sensitive nucleoside transporter and its role in gemcitabine sensitivity. Cancer Res 2000;60:6075-9.
19. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-

cell lung cancer. N Engl J Med 2002;346:92-8.
20. Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-8.
21. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-23.
22. Gridelli C, Shepherd FA. Chemotherapy for elderly patients with non-small cell lung cancer: a review of the evidence. Chest 2005;128:947-57.
23. Kasai T, Nakamura Y, Fukuda M, et al. A Phase II Study of S-1 for Previously Untreated Elderly Patients with Advanced Non-Small Cell Lung Cancer. Chemotherapy 2016;61:93-8.
24. Goto H, Okano Y, Machida H, et al. Phase II study of tailored S-1 monotherapy with a 1-week interval after a 2-week dosing period in elderly patients with advanced non-small cell lung cancer. Respir Investig 2018;56:80-6.
25. Masuda T, Watanabe M, Fujitaka K, et al. Alternate-day administration of S-1 for elderly patients with advanced non-small-cell lung carcinoma: A prospective feasibility study. Mol Clin Oncol 2018;9:539-44.
26. Imai H, Minemura H, Kishikawa T, et al. Efficacy and safety of S-1 monotherapy in previously treated elderly patients (aged ≥75 years) with non-small cell lung cancer: A retrospective analysis. Thorac Cancer 2020;11:2867-76.
27. Nokihara H, Lu S, Mok TSK, et al. Randomized controlled trial of S-1 versus docetaxel in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy (East Asia S-1 Trial in Lung Cancer). Ann Oncol 2017;28:2698-706.
28. Sugawara S, Nakagawa K, Yamamoto N, et al. Japanese subgroup analysis of a phase III study of S-1 versus docetaxel in non-small cell lung cancer patients after platinum-based treatment: EAST-LC. Int J Clin Oncol 2019;24:485-493.
29. Lai CL, Wei YF, Hsia TC, et al. S-1 plus cisplatin as first-line treatment of patients with advanced non-small cell lung cancer in Taiwan. Asia Pac J Clin Oncol 2020;16:e68-73.
30. Kubota K, Sakai H, Katakami N, et al. A randomized phase III trial of oral S-1 plus cisplatin versus docetaxel plus cisplatin in Japanese patients with advanced non-small-cell lung cancer: TCOG0701 CATS trial. Ann Oncol 2015;26:1401-8.
31. Kuyama S, Ochi N, Bessho A, et al. A phase II trial of carboplatin plus S-1 for elderly patients with advanced non-small-cell lung cancer with wild-type epidermal growth factor receptor: The Okayama Lung Cancer Study Group Trial 1202. Lung Cancer 2017;112:188-94.
32. Kaira K, Yanagitani N, Sunaga N, et al. Prospective exploratory study of gemcitabine and S-1 against elderly patients with advanced non-small cell lung cancer. Oncol Lett 2017;14:1123-8.
33. Yoshimura A, Chihara Y, Date K, et al. A Phase II Study of S-1 and Paclitaxel Combination Therapy as a First-Line Treatment in Elderly Patients with Advanced Non-Small Cell Lung Cancer. Oncologist 2019;24:459-e131.
34. Takayama K, Uchino J, Fujita M, et al. Phase I/II Study of Docetaxel and S-1 in Previously-Treated Patients with Advanced Non-Small Cell Lung Cancer: LOGIK0408. J Clin Med 2019;8:2196.
35. Chihara Y, Yoshimura A, Date K, et al. Phase II Study of S-1 and Paclitaxel Combination Therapy in Patients with Previously Treated Non-Small Cell Lung Cancer. Oncologist 2019;24:1033-e617.
36. Miyanaga A, Kubota K, Hosomi Y, et al. Phase II trial of S-1 plus cisplatin combined with bevacizumab for advanced non-squamous non-small cell lung cancer (TCOG LC-1202). Jpn J Clin Oncol 2019;49:749-54.
37. Kaira K, Imai H, Souma R, et al. An Exploratory Randomized Phase II Trial Comparing CDDP Plus S-1 With Bevacizumab and CDDP Plus Pemetrexed With Bevacizumab Against Patients With Advanced Non-squamous Non-small Cell Lung Cancer. Anticancer Res 2019;39:2483-91.
38. Nishino K, Imamura F, Kumagai T, et al. A randomized phase II study of bevacizumab in combination with docetaxel or S-1 in patients with non-squamous non-small-cell lung cancer previously treated with platinum based chemotherapy (HANSHIN Oncology Group 0110). Lung Cancer 2015;89:146-53.
39. Yamada K, Ichiki M, Takahashi K, et al. A multicenter phase II trial of S-1 combined with bevacizumab after platinum-based chemotherapy in patients with advanced non-squamous non-small cell lung cancer. Cancer Chemother Pharmacol 2016;78:501-7.
40. Nishijima-Futami Y, Minami S, Futami S, et al. Phase II study of S-1 plus bevacizumab combination therapy for patients previously treated for non-squamous non-small cell lung cancer. Cancer Chemother Pharmacol

2017;79:1215-20.
41. Xie XH, Wang F, Lin XQ, et al. Anlotinib Plus S-1 for Patients with EGFR Mutation-Negative Advanced Squamous Cell Lung Cancer with PS Scores of 2-3 After Progression of Second-Line or Later-Line Treatment. Cancer Manag Res 2020;12:12709-14.
42. Xiang M, Yang X, Ren S, 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 2021;26:e2130-5.
43. Zhou T, Wu C, Zhang C, et al. A retrospective study of low-dose apatinib combined with S-1 in patients with advanced non-small cell lung cancer. J Thorac Dis 2019;11:1831-7.
44. Chen S, Sun J, Zhao L, et al. Safety of apatinib plus S-1 for advanced solid tumor as palliative treatment. Exp Ther Med 2021;21:62.
45. Tamiya A, Tamiya M, Shiroyama T, et al. Phase II trial of carboplatin, S-1, and gefitinib as first-line triplet chemotherapy for advanced non-small cell lung cancer patients with activating epidermal growth factor receptor mutations. Med Oncol 2015;32:40.
46. Nakahara Y, Shimokawa T, Misumi Y, et al. Phase I/II study of erlotinib plus S-1 for patients with previously treated non-small cell lung cancer: Thoracic Oncology Research Group (TORG) 0808/0913. Invest New Drugs 2021;39:202-9.
47. Tamura N, Horinouchi H, Sekine K, et al. Efficacy of subsequent docetaxel +/- ramucirumab and S-1 after nivolumab for patients with advanced non-small cell lung cancer. Thorac Cancer 2019;10:1141-8.
48. Di Maio M, Chiodini P, Georgoulias V, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2009;27:1836-43.
49. Soria JC, Mauguen A, Reck M, et al. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. Ann Oncol 2013;24:20-30.
50. Nukatsuka M, Saito H, Nakagawa F, et al. Combination therapy using oral S-1 and targeted agents against human tumor xenografts in nude mice. Exp Ther Med 2012;3:755-62.
51. Chen CT, Yamaguchi H, Lee HJ, et al. Dual targeting of tumor angiogenesis and chemotherapy by endostatin-cytosine deaminase-uracil phosphoribosyltransferase. Mol Cancer Ther 2011;10:1327-36.
52. Herbst RS, O'Neill VJ, Fehrenbacher L, et al. Phase II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. J Clin Oncol 2007;25:4743-50.
53. Inagaki M, Shinohara Y, Kaburagi T, et al. S-1-containing chemotherapy for patients with non-small-cell lung cancer: A population-based observational study by the Ibaraki thoracic integrative (POSITIVE) research group. Mol Clin Oncol 2016;4:1025-30.
54. Okabe T, Okamoto I, Tsukioka S, et al. Synergistic antitumor effect of S-1 and the epidermal growth factor receptor inhibitor gefitinib in non-small cell lung cancer cell lines: role of gefitinib-induced down-regulation of thymidylate synthase. Mol Cancer Ther 2008;7:599-606.
55. Tanaka H, Tanzawa S, Misumi T, et al. A phase II study of S-1 and cisplatin with concurrent thoracic radiotherapy followed by durvalumab for unresectable, locally advanced non-small-cell lung cancer in Japan (SAMURAI study): primary analysis. Ther Adv Med Oncol 2022;14:17588359221142786.
56. Yamamoto H, Soh J, Okumura N, et al. Randomized phase II study of daily versus alternate-day administrations of S-1 for the elderly patients with completely resected pathological stage IA (tumor diameter > 2 cm)-IIIA of non-small cell lung cancer: Setouchi Lung Cancer Group Study 1201. PLoS One 2023;18:e0285273.

Cite this article as: Cao F, Gu C, Hong W, Jin Y. Advances in monotherapy and combination therapy of S-1 for patients with advanced non-small cell lung cancer: a narrative review. Transl Cancer Res 2024;13(4):2012-2025. doi: 10.21037/tcr-23-2019

