Phase II study of S-1 monotherapy as a first-line treatment for elderly patients with advanced nonsmall-cell lung cancer: the Central Japan Lung Study Group trial 0404

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Although S-1 has been shown to have activity against advanced nonsmall-cell lung cancer (NSCLC), its efficacy for elderly patients remains unclear. This phase II study evaluated the efficacy and safety of S-1 as a first-line treatment for elderly patients. Chemotherapy-naïve patients aged 70 years or older with stages IIIB to IV or postoperative NSCLC and performance status 1 or lower were eligible. Patients received S-1 approximately equivalent to 80 mg/m^2/day for 2 weeks followed by a 1-week rest period every 3 weeks. The primary end point was the response rate. Secondary end points were toxicity, disease control rate, progression-free survival, and overall survival. Twenty-nine patients were eligible. The median age was 78 years (range, 70–85 years). The overall response rate and the disease control rate were 27.6 [95% confidence interval (CI), 11.3–43.9%] and 65.5% (95% CI: 48.2–82.8%), respectively. The median progression-free survival time was 4.0 months (95% CI: 4.0–9.8 months). The median overall survival was 12.1 months (95% CI: 13.8–25.5 months) and the 1-year survival rate was 53.6%. No grade 4 toxicities were observed. The only hematological toxicity of grade 3 was anemia in 6.9% of patients. The grade 3 nonhematological toxicities included hyponatremia, anorexia, nausea, oral mucositis, and diarrhea in 3.4% of patients and infection in 6.9% of patients. S-1 monotherapy was effective and well tolerated as a first-line treatment for elderly patients with advanced NSCLC. The results of this study warrant further investigations of this regimen, including a randomized controlled trial. ***Anti-Cancer Drugs*** **22:811–816 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Approximately 80–85% of the patients have nonsmall-cell lung cancer (NSCLC), and most of them present with advanced disease at the time of diagnosis. More than 50% of patients diagnosed with advanced NSCLC are aged more than 65 years [2]. The median age at diagnosis is reportedly 70 years [3]. This leaves no doubt that lung cancer in older adults is becoming a common problem for oncologists.

Elderly patients are often excluded from clinical trials because they are simply old or have medical comorbidities and impairment of organ function. Therefore, the standard regimen for elderly patients with advanced NSCLC is not yet clear. However, third-generation monotherapy with vinorelbine or docetaxel is currently the treatment supported by prospective elderly specific phase III clinical trials [4–6]. Therefore, single-agent chemotherapy is usually recommended in clinical practice, although combination chemotherapy is sometimes selected for vigorous patients without any comorbidities, the so-called 'fit' elderly. It is apparent that single-agent chemotherapy with satisfactory effectiveness is preferable for elderly patients because the toxicity with monotherapy is generally milder than with a combination therapy.

S-1 is an orally active combination of tegafur, gimeracil, and oteracil in a molar ratio of 1 : 0.4 : 1 [7]. This agent has three different mechanisms of action. Tegafur is a

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prodrug converted by cells to fluorouracil, which has anticancer activity. Gimeracil is 5-chloro-2,4-dihydroxypyrimidine, which increases the plasma concentrations of fluorouracil by competitively inhibiting dihydropyrimidine dehydrogenase, which degrades fluorouracil [8]. Oteracil is distributed selectively to the small and large intestines after oral administration. It inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing its gastrointestinal toxic effects [9].

S-1 has been shown to have a marked activity against NSCLC and against a broad array of other solid tumors including gastric, colorectal, breast, cervical, and pancreatic cancers [10]. S-1 also has a great advantage in its convenience because the drug is an oral agent. The rate of response to treatment with S-1 was reported to be *22%* in patients with advanced NSCLC of less than 75 years [11]. However, the activity of this drug in elderly patients remains unclear. In this context, we carried out this prospective phase II study to evaluate the efficacy and safety of S-1 as a first-line treatment for elderly patients with advanced NSCLC.

Methods

Patient eligibility

Elderly chemotherapy-naïve patients (age $\geq$ 70 years) with stages IIIB–IV (the new Union for International Cancer Control criteria version 7) or recurrence of postoperative NSCLC were eligible for this study. They had histologically or cytologically confirmed NSCLC, with at least one measurable lesion. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0–1 and an estimated life expectancy of more than 3 months. Adequate organ function was required, as was a hemoglobin count of more than or equal to 9 g/dl, white blood cell count of 3500/μl but less than or equal to 12 000/μl, absolute neutrophil count of more than or equal to 2000/μl, platelet count of more than or equal to 100 000/μl, aspartate aminotransferase and alanine aminotransferase of less than or equal to 100 IU/l, total bilirubin of less than or equal to 1.5 mg/dl, serum creatinine of less than or equal to 1.5 mg/dl, and pressure of arterial oxygen of more than or equal to 60 mmHg. Patients with symptomatic brain metastasis or severe comorbidity, such as unstable cardiovascular disease, uncontrolled diabetes, or active infection, were excluded. Patients with pulmonary fibrosis detected on chest radiograph were also excluded. The institutional review board of each institution approved this study. Written informed consent was obtained from all enrolled patients.

Drug administration

S-1 was prescribed according to the body surface area (BSA) to provide a dose approximately equivalent to 80 mg/m^2/day as follows: BSA of less than 1.25 m^2, 80 mg daily; BSA of more than or equal to 1.25 m^2 but less than 1.5 m^2, 100 mg daily; and BSA of more than or equal to 1.5 m^2, 120 mg daily. One cycle consisted of consecutive administration of S-1 for 14 days followed by a 1-week rest period. This 3-week cycle was repeated until confirmation of progressive disease (PD), intolerable toxicity, or withdrawal of consent. When the creatinine clearance was less than 50 but more than or equal to 30 ml/min, the dose of S-1 was decreased by one level as follows: 120 to 100, 100 to 80, and 80 to 50 mg/m^2/day. If toxicity was observed, the dose could also be decreased by one level as described above in the next course. Second-line chemotherapy or other treatments after S-1 were not prohibited by the protocol.

Response and toxicity evaluation

The objective tumor responses were assessed as complete response (CR), partial response (PR), stable disease, or PD in accordance with the Response Evaluation Criteria in Solid Tumors criteria [12]. Baseline assessment was made within 28 days before the treatment. During the treatment, assessments were made as a rule every 4 weeks until disease progression. Toxicity was graded by the National Cancer Institute of Common Toxicity Criteria (version 3.0) at each cycle for each patient [13].

Statistical analysis

The primary end point of this study was a response rate (RR) defined as the proportion of patients whose best response was CR or PR among all eligible patients. Simon's two-stage optimum design was used to determine the sample size and interim decision criteria. Assuming that a RR of *20%* in eligible patients would indicate potential usefulness, whereas a RR of 5% would be the lower limit of interest, with an α error of 0.05 and an β error of 0.2, the required number of patients was 29. Assuming noneligible patients would be registered, the actual accrual number was determined to be 30. This regimen would be rejected when no patient had an objective response at the interim analysis with the first 10 patients.

Secondary end points of this study were toxicity, disease control rate, progression-free survival (PFS), and overall survival (OS). A disease control rate was defined as the proportion of patients whose best response was CR or PR, or stable disease among all eligible patients. PFS was defined as the interval between the start of the treatment and the date of the first observation of disease progression or death from any cause. OS was defined as the interval between the initial registration and the date of death from any cause. The PFS and OS distribution were estimated by the Kaplan–Meier method. The comparison of OS between two groups was done with the log-rank test. A *P* value of less than 0.05 was considered to be significant.

Results

Patient characteristics

From April 2005 to February 2009, 30 patients were enrolled from eight institutes. One patient was excluded

as ineligible because he was shown to have prostate cancer before the treatment and the drug was not administered. The characteristics of the remaining 29 patients are listed in Table 1. Twenty-two patients were men, representing 75.9% of all eligible patients. The median age was 78 years (range, 70–85 years). Eight patients (27.6%) had Eastern Cooperative Oncology Group performance status of 0, and 21 patients (72.4%) had Eastern Cooperative Oncology Group performance status of 1. Seven patients (24.1%) had stage IIIB disease, 21 patients (72.4%) had stage IV, and the remaining patient had postoperative recurrence. Eighteen patients (62.1%) had adenocarcinoma, seven patients (24.1%) had squamous cell carcinoma, and four patients (13.8%) had other types of NSCLC.

Response and survival

The objective tumor responses are listed in Table 2. The overall RR and disease control rate were 27.6 [95% confidence interval (CI), 11.3–43.9%] and 65.5% (95% CI: 48.2–82.8%), respectively. Two patients were not evaluated for response because both of them had pneumonia (grade 3) after one cycle of the treatment. The median follow-up period was 12.1 months (range, 0.8–53.2 months), and all the patients had already completed chemotherapy with S-1 at the data cutoff point (January 2010). The median PFS time was 4.0 months (95% CI: 4.2–10.0 months) (Fig. 1). The median OS was 12.8 months (95% CI: 13.8–25.5 months; Fig. 2) and the 1-year survival rate was 53.6%.

Data on epidermal growth factor receptor (EGFR) mutation status were collected retrospectively. It was found that histological specimens had been examined for EGFR mutations in 12 patients. Among these 12 patients, EGFR mutation was found in five patients, an exon 19 deletion in two patients, and the L858R point

Table 1 **Patient characteristics**

Characteristics	No of patients (%)
Age (years)	Median 78 (range: 70–85)
Male/female	22/7 (75.9/24.1)
Smoking status	
Current	9 (31.0)
Former	14 (48.3)
Never	6 (20.7)
ECOG performance status	
0	8 (27.6)
1	21 (72.4)
Stage of disease	
IIIB	7 (24.1)
IV	21 (72.4)
Recurrent	1 (3.4)
Histology	
Adenocarcinoma	18 (62.1)
Squamous cell carcinoma	7 (24.1)
Other	4 (13.8)

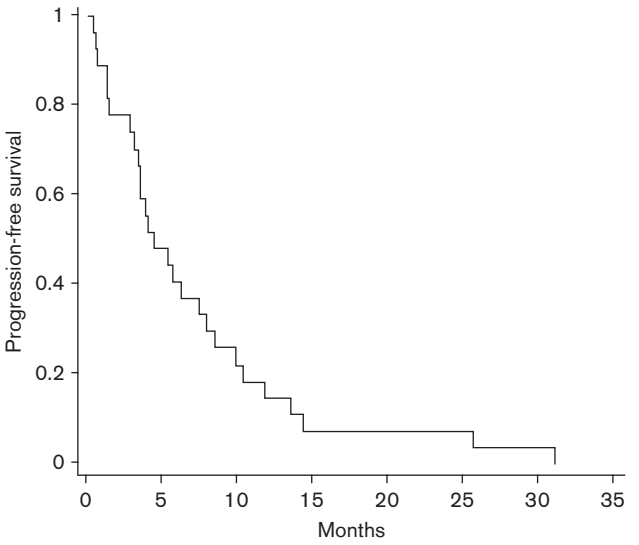
ECOG, Eastern Cooperative Oncology Group.

Table 2 **Response**

Response	No of patients	Percentage	95% CI
Complete response	0	0	
Partial response	8	27.6	
Stable disease	11	37.9	
Progressive disease	8	27.6	
Not evaluated	2	6.9	
Overall response	8	27.6	11.3–43.9
Disease control rate	19	65.5	48.2–82.8

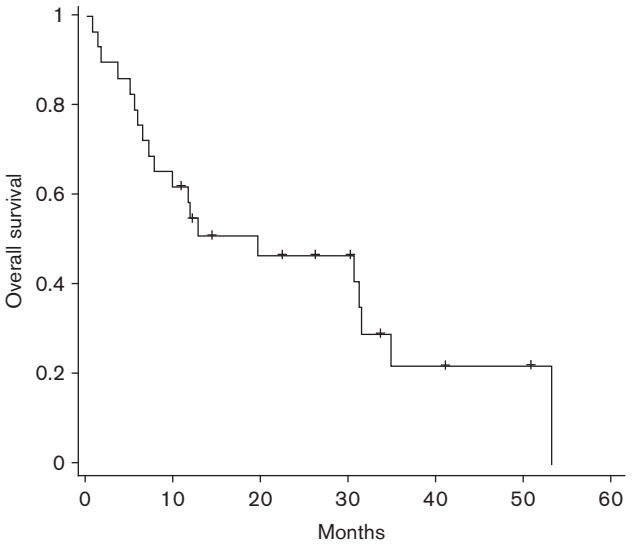
CI, confidence interval.

Fig. 1



Progression-free survival curves for patients treated with S-1 ($N=29$). There was no censored patient at the data cutoff point.

Fig. 2



Overall survival curves for patients treated with S-1 ($N=29$). Crosses indicate censored patients at the data cutoff point.

Table 3 Adverse events (*N*=29)

Toxicities	No. of patients				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Hematological					
Leukopenia	4	1	0	0	0 (0)
Neutropenia	7	1	0	0	0 (0)
Hemoglobin	5	2	2	0	2 (6.9)
Thrombocytopenia	5	1	0	0	0 (0)
Nonhematological					
AST/ALT	4	0	0	0	0 (0)
Bilirubin	2	1	0	0	0 (0)
Creatinine	6	0	0	0	0 (0)
Hyponatremia	11	0	1	0	1 (3.4)
Fatigue	7	2	0	0	0 (0)
Anorexia	6	2	1	0	1 (3.4)
Nausea	1	2	1	0	1 (3.4)
Vomiting	1	0	0	0	0 (0)
Oral mucositis	1	1	1	0	1 (3.4)
Diarrhea	1	1	1	0	1 (3.4)
Constipation	3	1	0	0	0 (0)
Infection	1	0	2	0	2 (6.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

mutation in three patients. Significant differences were not observed in the RR, PFS, and, OS between patients with and without EGFR mutation (data not shown).

Feasibility

Overall, 29 patients were assessed for hematological and nonhematological toxicities, which are listed in Table 3. The only hematological toxicity of grade 3 was anemia, which was observed in two patients (6.9%). No grade 4 hematological toxicities were observed. The grade 3 nonhematological toxicities included hyponatremia, anorexia, nausea, oral mucositis, and diarrhea in one patient (3.4) and infection (pneumonia) in two patients (6.9%). Anorexia, nausea, and diarrhea of grade 3 were observed in the same patient. No grade 4 nonhematological toxicities were observed.

Cycles administered

The median number of cycles that were administered was 3 (range, 1–19). The reasons for discontinuation of treatment were progression of disease in 17 patients (58.6%), toxicities in nine patients (31.0%), the patient's request one case (3.6%), and the doctor's decision in two patients (6.9%), respectively.

Treatment after protocol discontinuation

Data on treatments after the study protocol were also collected retrospectively. Among the 29 patients, doublet chemotherapy was administered in seven patients (carboplatin and paclitaxel in six, and carboplatin and pemetrexed in one), single-agent therapy in six patients (paclitaxel in one, vinorelbine in three, and docetaxel in two), and EGFR tyrosine kinase inhibitor (TKI) in four patients (erlotinib) as a second-line treatment. Twelve patients did not receive any second-line treatment. Three patients received EGFR–TKI therapy as a third-line or later treatment (gefitinib in one and erlotinib in two patients). There was a significant difference in OS between patients who received any second-line treatment and those who did not (median OS: 22.3 vs. 6.9 months, $P = 0.0015$). As for EGFR–TKI treatment, there was a trend toward longer OS in patients who received any EGFR–TKI after S-1 therapy compared with those who did not (median OS: 30.2 vs. 11.7 months, $P = 0.09$), although it was not statistically significant.

Discussion

This phase II study was designed to evaluate the efficacy and toxicity of S-1 monotherapy as a first-line treatment for elderly patients with advanced NSCLC. It was shown that the overall RR and the disease control rate were 27.6 and 65.5%, respectively. The median PFS time was 4.0 months and the median OS was 12.8 months. These results were comparable with or better than those seen in earlier studies with single-agent chemotherapies using vinorelbine or docetaxel, which are recognized to be one of the standard regimens for elderly patients [4–6]. In the Multicenter Italian Lung Cancer in the Elderly study, which is one of the representative phase III studies for elderly patients with NSCLC, the overall tumor response, median PFS time, and the median OS time with vinorelbine monotherapy were reported to be 18% (95% CI: 13–23%), 18 (95% CI: 13–20 weeks), and 36 weeks (95% CI: 30–45 weeks), respectively [5]. The West Japan Thoracic Oncology Group 9904 trial, which is another phase III study of monotherapy for elderly patients, showed the RR of 22.7 (95% CI: 13.9–31.5%) and 9.9% (95% CI: 3.8–16.0%) in the docetaxel and vinorelbine group, respectively. The median PFSs were reportedly 5.5 and 3.1 months, and the median OS were 14.3 and 9.9 months in each group, although 95% CI values were not available [6]. The overall RR of 27.6% achieved in this study of S-1 monotherapy was superior to those in the earlier studies, although this was a phase II study. The median PFS of 4.0 months for S-1 is also comparable with earlier studies.

The toxicity profile for S-1 therapy was generally mild and tolerable. No grade 4 toxicity was observed. Grade 3 toxicities consisted of anemia (6.9%), hyponatremia (3.4%), anorexia (3.4%), nausea (3.4%), oral mucositis (3.4%), diarrhea (3.4%), and pneumonia (6.9%). Anorexia, nausea, and diarrhea were observed in the same patient. These findings show that the incidence of toxicities of grades 3–4 for S-1 monotherapy is quite low. In particular, no hematological toxicities, such as leucopenia, neutropenia, and thrombocytopenia of grades 3–4 were observed. This good feasibility deserves special mention, because even vinorelbine, which is considered to be a mild agent compared with other drugs, showed more than 30% grade 3–4 toxicities in the West Japan Thoracic Oncology Group 9904 study [6].

Originally, the treatment regimen of a 4-week administration followed by a 2-week rest period was reported in terms of S-1 therapy [11]. However, we adopted the regimen of a 2-week administration and a 1-week rest, because a 3-week cycle has been frequently used as a chemotherapy regimen for patients with lung cancer. This is reasonable because the dose of S-1 administered in the 6-week period is the same in both regimens, and the similar pharmacokinetic profile was already reported [14]. Adopting the 3-week cycle regimen might result in a low toxicity profile in this study.

S-1 is easy to administer because it is an oral agent. Daily administration is another benefit because it can be easily stopped when severe toxicity occurs. Given these advantages and the good efficacy and feasibility observed in this study, S-1 monotherapy is quite suitable for elderly patients, although the survival benefit should be confirmed in a phase III trial.

There has been some argument as to which is better, single-agent monotherapy or combination therapy of two drugs for elderly patients with NSCLC. Although the RR is better in combination chemotherapies, the toxicities are milder in monotherapies. Favorable results have been reported for combination chemotherapies [15], but negative outcomes are also reported [5]. Although advanced age alone does not preclude combination chemotherapies [16], age should still be taken into consideration when selecting appropriate chemotherapy in a clinical setting given the increased likelihood of comorbidities. If a favorable response and survival outcome can be obtained, monotherapy is evidently preferable because of milder toxicities. In this sense, the results in this study are encouraging. Therefore, a phase III trial should be planned to confirm the survival benefit of the S-1 monotherapy for elderly patients.

Some limitations of this study should be mentioned. First, the patients recruited were relatively few. However, the sample size was calculated according to previously reported RRs in studies of elderly patients with NSCLC. Furthermore, the RR of 27.6% in this study was above the RR targeted beforehand. Therefore, we think that the statistic power of detection for the efficacy of S-1 was robust. Second, the median number of treatment cycles that were administered was 3, which was relatively low. Seven of 29 patients received only one cycle of treatment. The reasons for stopping the treatments in these seven were PD in three patients and grade 3 toxicity in two patients. Therapy for the other two patients was discontinued due to only grade 1–2 toxicities. Chances are that other patients also stopped the therapy due to relatively mild gastrointestinal toxicities even in later cycles and as a result the median number of treatment cycles administered became small. The reason for the relatively few administered cycles is not clear. One possibility is that elderly patients easily complained of discomfort due to mild toxicities. If more cycles were administered by adjusting the dose of S-1 or using some antiemetics, the results might be different. However, given that this regimen was for elderly patients, the cycles of treatment might not have necessarily resulted in a better outcome. Finally, EGFR mutation status was not examined in all patients. EGFR–TKI treatment after S-1 therapy might affect the OS, because patients with NSCLC with EGFR mutation can respond to TKI therapy, and their OS would be prolonged [17,18]. However, the relatively good overall RR and PFS in this study underscore the effectiveness of S-1 monotherapy for elderly patients with NSCLC.

In conclusion, S-1 monotherapy was effective and well tolerated as a first-line treatment for elderly patients with advanced NSCLC. The result of this study warrants further investigations of this regimen, including a randomized controlled trial.

Acknowledgements

Conflicts of interest

None declared.

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