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Pharmacokinetic study of weekly (days 1-5) low-dose S-1 in patients with non-small-cell lung cancer

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Running Title: Weekly low-dose S-1 for NSCLC

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Abstract

Background. S-1, an oral fluoropyrimidine, is usually given for 4 weeks (80 mg/m^2/day) followed by a 2-week rest. However, compliance with this regimen is unsatisfactory because of adverse events such as leukopenia, anorexia, and nausea. To reduce adverse effects and improve compliance, we studied a "5-day on/2-day off" low-dose regimen of S-1 and evaluated pharmacokinetics in patients with non-small-cell lung cancer (NSCLC).

Methods. Twelve patients with NSCLC were divided into 2 groups and received S-1 in a dose of 25 mg twice daily (level 1, n = 6) or 40 mg twice daily (level 2, n = 6) for 5 consecutive days followed by a 2-day rest (5 days on/2 days off) every week. Plasma 5-fluorouracil (5-FU) concentrations were measured.

Results. The maximum concentration in plasma and the area under the plasma concentration-time curve from 0 to 9 h were respectively 55.3 ± 21.1 ng/ml and 290.2 ± 95.7 ng・hr/ml for level 1, as compared with 104.2 ± 33.5 ng/ml and 541.9 ± 232.3 ng・hr/ml for level 2. These values were similar to those previously reported for a continuous intravenous infusion of 5-FU. Adverse events were grade 1 fatigue (n = 1 in each group) and anorexia (n = 1 in each group).

Conclusions. A "5-day on/2-day off" low-dose (40 mg twice daily) regimen of S-1 is feasible for the treatment of NSCLC, with acceptable plasma 5-FU concentrations and minimal adverse effects. A phase II or III trial of this regimen in an adjuvant setting is warranted in patients with NSCLC.

Keywords: chemotherapy, low-dose administration, non-small-cell lung cancer, oral anticancer fluoropyrimidine agent, pharmacokinetic study, S-1.

TEXT

Introduction

Lung cancer is the leading cause of cancer-related mortality in many countries [1]. For non-small-cell lung cancer (NSCLC), adjuvant chemotherapy is recommended after complete resection in patients with pathological stage IB to IIIA disease. The West Japan Study Group for Lung Cancer Surgery reported that survival after complete resection was significantly prolonged by adjuvant treatment with oral uracil-tegafur (UFT) as compared with observation alone in patients with stage I, II, or III NSCLC [2]. Adjuvant chemotherapy with UFT for 2 years was also shown to improve survival in patients with completely resected pathological stage I adenocarcinoma of the lung [3]. Although another study [4] showed no significant improvement in the postoperative survival of patients with pathological stage I NSCLC, a meta-analysis reported that postoperative adjuvant chemotherapy with UFT prolonged 5- and 7-year survival in Japanese patients who primarily had pathological stage I adenocarcinoma of the lung [5].

S-1 is an oral anticancer fluoropyrimidine agent that combines the 5-fluorouracil (5-FU) prodrug tegafur with two enzyme inhibitors, 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate [6]. CDHP inhibits dihydropyrimidine dehydrogenase, and potassium oxonate suppresses pyrimidine phosphoribosyltransferase. Consequently, 5-FU concentrations after oral administration of S-1 are higher than those after than a protracted intravenous infusion of 5-FU given at a dose equimolar to the tegafur in S-1, with no increase in the incidence of gastrointestinal toxicity [7, 8]. S-1 is usually given for 4 weeks (80 mg/m^2/day) followed by a 2-week rest. However, compliance with regimen is often unsatisfactory

because of adverse events such as anorexia, nausea, and leukopenia [9, 10]. To reduce adverse effects and improve compliance, we studied a "5-day on/2-day off" low-dose regimen of S-1 and evaluated pharmacokinetics in patients with non-small-cell lung cancer (NSCLC).

Patients and Methods

Patient eligibility

All patients were enrolled at the Department of Thoracic Surgery, Kyoto University Hospital. Eligible patients had histopathologically proven, completely resected lung cancer (pathological stage I, II, or IIIA) and a performance status (Eastern Cooperative Oncology Group) of 0 or 1. Recurrent disease after complete resection was included. The hematological criteria for enrollment were as follows: leukocyte count, $\geq$4,000/mm^3; neutrophil count, $\geq$2,000/mm^3; platelet count, $\geq$100,000/mm^3; hemoglobin concentration, $\geq$10.0 g/dl; serum bilirubin concentration, $\leq$1.5 mg/dl; serum aspartate aminotransferase and alanine aminotransferase concentrations, no more than twice the upper limit of normal; serum creatinine concentrations, $\leq$1.5 mg/dl; creatinine clearance, $\geq$60 ml/min or higher; and life expectancy, $\geq$3 months. The protocol was approved by our institutional review board, and each patient gave written informed consent (approved by Kyoto University Graduate School and Faculty of Medicine**,** Ethics Committee, registration number C-74).

Treatment schedule

S-1 was administered orally twice daily, after breakfast and dinner. For each cycle of treatment, S-1 was given for 5 consecutive days followed by a 2-day rest (5

days on/2 days off) for 4 weeks. Patients received S-1 in a dose of 25 mg twice daily (level 1) or 40 mg twice daily (level 2). Treatment was repeated until the development of disease progression or unacceptable toxicity. Patients had to have a leukocyte count of $\geq$3,000/mm^3, a neutrophil count of $\geq$1,500/mm^3, and a platelet count of $\geq$75,000/mm^3 to receive the next cycle of treatment. If grade 2 or higher hematologic or nonhematologic toxicity occurred during any treatment cycle, S-1 was discontinued and withheld until such toxicity resolved. The eligibility criteria for study entry had to be met before the resumption of treatment.

Specimen collection to assess 5-FU concentrations in plasma

Peripheral blood samples were collected on day 5, before treatment in the morning and 2, 4, and 9 h after treatment. Peripheral blood samples (8 ml per sample) were collected into heparinized tubes and centrifuged at 3,000 rpm for 10 min at 5˚C; the plasma was separated and samples were stored at -20˚C.

Drug assay

Concentrations of 5-FU were analyzed as described by Matsushima et al. [11]. Tegafur was extracted with dichloromethane from each sample and analyzed using a high-performance liquid chromatograph equipped with an ultraviolet absorption spectrometer. 5-FU was extracted with ethyl acetate from the residue obtained after dichloromethane extraction. It was then analyzed using a negative ion chemical ionization-gas chromatograph/mass spectrometer.

Pharmacokinetic parameters

Standard pharmacokinetic parameters of 5-FU were calculated on the basis of the plasma concentration-time profiles obtained from the 4 samples for each patient who received level 1 (S-1 25 mg) or level 2 (S-1 40 mg). Calculations were done with a non-compartmental method, using the computer program WinNonlin, version 5.2 (Pharsight Corporation, Mountain View, CA, USA). The maximum concentration in plasma (C_{max}) was obtained directly from the concentration-time data. The area under the plasma concentration-time curve was calculated using the trapezoidal rule from 0 to 9 h (AUC_{0-9}). The values are expressed as the means ± standard deviation (SD) for the 6 patients per group.

Evaluation of toxicity

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, Version 3.0.

Results

Patient characteristics

Twelve patients were enrolled in this study and divided into 2 groups (level 1, 6 patients; level 2, 6 patients). The characteristics of the patients are shown in Table 1-1. Five of the 6 patients given level 1 and 3 of the 6 patients given level 2 had recurrent disease at study entry. All 8 of these patients with recurrent disease had previously received at least one other regimen of chemotherapy (Table 1-2). The other 4 patients did not have recurrent disease or a history or prior chemotherapy at study entry. The mean daily dose per body surface area (BSA) was 33.6 mg/m^2 (25.2 - 41.4 mg/m^2) for level 1 and 47.8 mg/m^2 (43.5 - 56.4 mg/m^2) for level 2.

Pharmacokinetics of 5-FU after S-1 administration

The time courses of plasma 5-FU concentrations in the level 1 and 2 groups are shown in Fig. 1. On the basis of plasma 5-FU concentrations, Cmax and AUC_{0-9} were respectively 55.3 ± 21.1 ng/ml and 290.2 ± 95.7 ng・hr/ml at level 1, as compared with 104.2 ± 33.5 ng/ml and 541.9 ± 232.3 ng・hr/ml at level 2 (Table 2).

Toxicity

Grade 1 fatigue (n=1 in each group) and anorexia (n=1 in each group) occurred as adverse events (Table 3).

Compliance

In the level 1 group (25 mg twice daily), S-1 treatment was discontinued because of progressive disease in 3 of the 6 patients at weeks 16, 35, and 60, respectively. All 3 of these patients had recurrent disease at study entry. One patient refused to continue S-1 treatment because of grade 1 fatigue at week 43, and another refused S-1 treatment at week 2 despite no toxicity. One patient continued to receive S-1 for more than 68 weeks with no adverse events. This patient (stage IIB) was the only one without recurrent disease at study entry in the level 1 group and has not shown any signs of recurrence at the time of this writing.

At level 2 (40 mg twice daily), S-1 was discontinued because of progressive disease in 2 of 6 patients at weeks 4 and 15, respectively. These 2 patients had recurrent disease at study entry. Another patient refused to continue treatment with S-1 because of grade 1 fatigue at week 12. The 3 other patients continued to receive S-1 without any

adverse events for more than 35, 44, and 51 weeks, respectively. These patients, who had pathological stage IB, IIIA, and IIIA, respectively, did not have recurrent disease at study entry and have not shown any signs of recurrence. Thus, all 4 patients without recurrent disease at study entry continued to receive S-1 without recurrence or adverse events for 35 to 68 weeks.

Discussion

Although UFT is effective as postoperative adjuvant chemotherapy in early-stage NSCLC, its efficacy for advanced disease remains to be confirmed [12]. In patients with completely resected pathological stage II to IIIA NSCLC, cisplatin-based chemotherapy is recommended for adjuvant chemotherapy on the basis of the results of randomized controlled trials [13-16]. In one study, however, the significant improvement in 5-year survival with cisplatin-based chemotherapy was not maintained after longer follow-up, mainly because a rise in noncancer-related mortality in patients who received cisplatin [17]. Thus, concern about late toxicity associated with cisplatin-based chemotherapy has highlighted the need for less toxic chemotherapy in a postoperative adjuvant setting. As stated above, S-1 is usually given daily for 4 weeks (80 mg/m^2/day) followed by a 2-week rest, repeated for 4 cycles. However, compliance with this regimen is often not satisfactory because of adverse events such as anorexia, nausea, and leukopenia. In one Japanese Phase II trial [10] of S-1 alone administered according to this schedule to 59 eligible patients with advanced lung cancer, grade 3 or higher toxicity included anorexia in 6 patients (10.2%), diarrhea in 5 (8.5%), neutropenia in 4 (6.8%), and malaise in 4 (6.8%). Only 10 (16.9%) of the 59 patients completed the fourth cycle of chemotherapy as scheduled, and toxicity was the reason

for treatment withdrawal in 7 of the 28 patients who received only one cycle of S-1. Recently, Yano et al. reported a feasibility study of postoperative adjuvant chemotherapy with S-1 in patients with NSCLC [18]. Each treatment cycle consisted of S-1 in a dose of 80 to 120 mg/day (80 mg/m^2/day) for 2 weeks followed by a 1-week rest. Patients were scheduled to receive 8 cycles of chemotherapy. The total and daily doses of S-1 in their study were similar to those in other studies [9, 10]. Eight courses of chemotherapy were completed as scheduled by 17 (56.7%) of the 30 patients. The completion rate of chemotherapy was only 42.9% in patients 70 years or older, as compared with 78.6% in those younger than 70 years. The compliance rate in the elderly patients is considered low for adjuvant chemotherapy. It thus remains unclear whether the recommended dose and treatment schedule for S-1 in an adjuvant setting should be the same as that for patients with advanced disease.

Ideally, drugs and treatment schedules used for postoperative adjuvant chemotherapy should have low toxicity and good compliance. Sakuramoto et al. [19] demonstrated that S-1 is an effective adjuvant treatment in patients with curatively resected gastric cancer as compared with surgery alone in a large randomized trial performed in Japan. In that study, S-1 (80 mg/m^2/day) was given for 4 weeks followed by a 2-week rest. Although overall survival was significantly better in the S-1 group, grade 3 or 4 adverse events such as anorexia, nausea, and leukopenia were more common in the S-1 group than in the surgery alone group. Among 517 patients scheduled to receive S-1 for 12 months, 71 (13.7%) refused to continue treatment because of adverse events or other factors, and 72 (13.9%) discontinued treatment at the investigators' discretion because of adverse events or complications. Overall, the dose of S-1 was decreased in 219 of the 517 patients (42.4%) who received S-1, as well as in

158 (46.5%) of the 340 patients who continued S-1 treatment for 12 months. On the basis of these results, we decided to evaluate a new regimen of S-1 designed to decrease adverse events and improve compliance. We not only lowered the daily dose of S-1 to 50 or 80 mg/day, but also used a "5-day on/2-day off" treatment schedule. At level 2 (80 mg/day) the Cmax of 5-FU was 104.2 ± 33.5 ng/ml and the AUC_{0-9} was 541.9 ± 232.3 ng・hr/ml. A pharmacokinetic study of S-1 at a standard dose of 80 mg/m^2/day in patients with advanced cancer (gastric, colorectal, and breast) [20] reported that the Cmax of 5-FU was 128.5 ± 41.5 ng/ml with an AUC_{0-14} of 723.9 ± 272.7 ng・hr/ml. Since dosage forms of S-1 was 40 mg and 25 mg, two dosage levels of low dose S-1, 80 mg/day (40 mg, twice a day) and S-1 50 mg/day (25 mg, twice a day) was used in this study. Although the dose of S-1 in our study was lower than the standard dose, our pharmacokinetic analysis showed that Cmax and AUC were comparable to those in patients who received a standard regimen of S-1. Moreover, in another pharmacokinetic study in patients with advanced colorectal cancer who received 5-FU (300 mg/m^2/day) by continuous venous infusion for 26 weeks [21], the 5-FU concentration at steady state was 94 ± 25 ng/ml, which was also similar to the Cmax of level 2 (104.2 ± 33.5 ng/ml) in the present study.

In conclusion, our results show that a "5-day on/2-day off" low-dose regimen of S-1 (40 mg, twice daily) is feasible for the treatment of NSCLC, with acceptable plasma 5-FU concentrations and minimal adverse effects. A phase II or III trial of this regimen in an adjuvant setting is warranted in patients with NSCLC.

Conflict of interest

The authors have no conflict of interest.

Figure legend

Fig. 1. Plasma concentrations of 5-FU after a single dose of S-1. * as a single dose.

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Table 1-1. Patient characteristics

	Level 1 (S-1 25 mg, twice daily)	Level 2 (S-1 40 mg, twice daily)
Enrolled patients	6	6
Age, years		
Median	79.2	65.3
Range	60-87	61-75
Sex		
Male/Female	3/3	5/1
ECOG performance status		
0/1	5/1	6/0
Stage		
IA (with recurrence)	3 (3)	1 (1)
IB (with recurrence)	1 (1)	2 (1)
IIA (with recurrence)	0 (0)	0 (0)
IIB (with recurrence)	1 (0)	0 (0)
IIIA (with recurrence)	1 (1)	3 (1)
Type of Surgery		
Pneumonectomy/Lobectomy/Segmentectomy/Partial*	0/4/1/1	1/3/2/0
Histology		
Adeno/ Squamous/ Large	4/1/1	4/2/0
Average daily dose per BSA** (mg/m^2)	33.6 (25.2 - 41.4)	47.8 (43.5 - 56.4)

*Partial: partial resection, **BSA: body surface area

Table 1-2. Characteristics of patients with recurrent disease at study entry

	Onset of recurrent disease after surgery (months after operation)	Recurrent site	Previous chemotherapies (as adjuvant or for recurrent disease)
Level 1 (S-1 25 mg, twice daily, n = 5)			
Patient 1 (79 y.o, female)	22	Local (pleura)	UFT as adjuvant, UFT+GEM, gefitinib for recurrence
Patient 2 (84 y.o, female)	11	Local (lung)	CBDCA, UFT, gefitinib for recurrence
Patient 3 (87 y.o, male)	13	Local (lung)	UFT as adjuvant, VNR for recurrence
Patient 4 (87 y.o, female)	68	Local (lung)	UFT as adjuvant, gefitinib for recurrence
Patient 5 (60 y.o, male)	30	Distant (brain)	CBDCA + PAC, UFT as adjuvant
Level 2 (S-1 40 mg, twice daily, n = 3)			
Patient 1 (62 y.o, female)	36	Local (lung)	UFT as adjuvant
Patient 2 (75 y.o, male)	5	Loco-regional (lymph nodes, pleura)	CBDCA+GEM, DOC, VNR or recurrent disease)
Patient 4 (61 y.o, male)	6	Distant (retroperitoneal)	CDDP+VNR as adjuvant, Doc for recurrence

GEM: Gemcitabine, CBDCA: Carboplatin, VNR: Vinorelbine, PAC: Paclitaxel, DOC: Docetaxel, CDDP: cisplatin.

Table 2. Pharmacokinetic parameters

	AUC0-9 (ng·hr/mL)	Cmax (ng/mL)	BSA (m^2)	AUC0-9/BSA (ng·hr/mL/m^2)
Level 1 (S-1 25 mg*)	290.2 ±95.7	55.3 ±21.1	1.524 ±0.270	200.6 ±87.2
Level 2 (S-1 40 mg*)	541.9 ±232.3	104.2 ±33.5	1.688 ±0.164	335.7 ±186.5

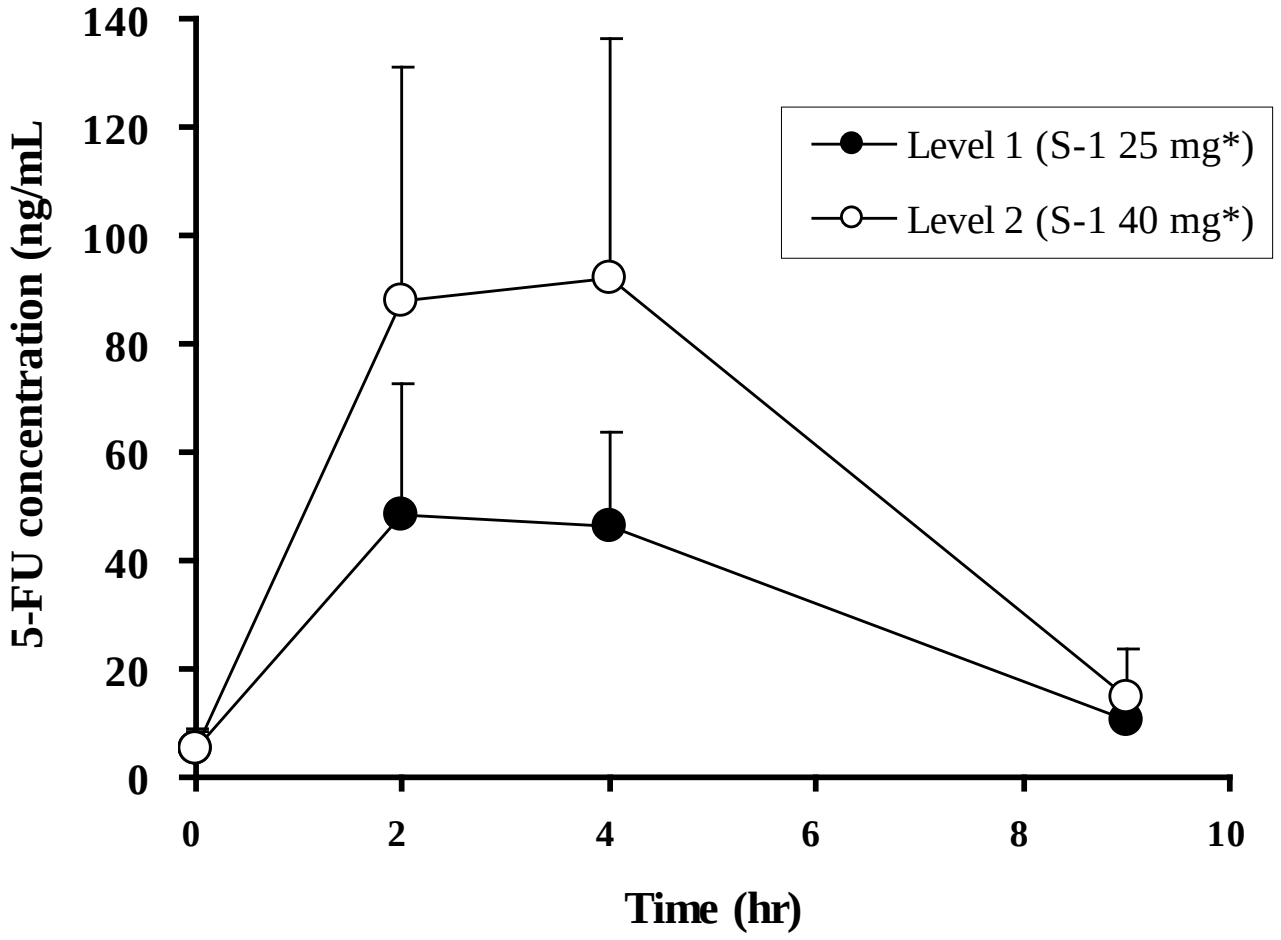
* as a single dose

Table 3. Toxicity

NCI-CTC grade	Level 1 (S-1 25 mg, twice daily)				Level 2 (S-1 40 mg, twice daily)				Level 1-2
	1	2	3	4	1	2	3	4	Grade 3/4
Hematologic									
Leukopenia	0	0	0	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	0	0	0	0
Anemia	0	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	0
Nonhematologic									
Anorexia	1	0	0	0	1	0	0	0	0
Nausea/Vomiting	0	0	0	0	0	0	0	0	0
AST/ALT	0	0	0	0	0	0	0	0	0
General fatigue	1	0	0	0	1	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0

Toxicities were graded according to the National Cancer Institute toxicity criteria (NCI-CTC) during chemotherapy

Fig. 1


140
120
100
80
60
40
20
0
5-FU concentration (ng/mL
0
2
4
6
8
10
Time (hr)
Level 1 (S-1 25 mg*)
Level 2 (S-1 40 mg*)