

ORIGINAL

A feasibility study of postoperative adjuvant chemotherapy with fluoropyrimidine S-1 in patients with stage II-IIIa non-small cell lung cancer

Mitsuhiro Tsuboi¹, Kazuya Kondo², Hiromitsu Takizawa¹, Naoya Kawakita¹, Toru Sawada¹, Hiroaki Toba¹, Yukikiyo Kawakami¹, Mitsuteru Yoshida¹, Hisashi Ishikura³, Suguru Kimura⁴, and Akira Tangoku¹

¹Department of Thoracic, Endocrine Surgery and Oncology, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramotocho, Tokushima City, Tokushima Pref. 770-8503, Japan, ²Department of Oncological Medical Services, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramotocho, Tokushima City, Tokushima Pref. 770-8503, Japan, ³Department of general thoracic surgery, Tokushima Red Cross Hospital, 103 Irinokuchi, Komatsushima City, Tokushima Pref. 773-8502, Japan, ⁴Department of surgery, East Tokushima Medical Center, 1-1 Oteraomukaikita, Itanocho, Itano-gun, Tokushima Pref. 779-0105, Japan

Abstract : Background : Adjuvant chemotherapy with uracil tegafur (UFT) improved survival among patients with completely resected stage I lung adenocarcinoma. S-1, an oral dihydropyrimidine dehydrogenase (DPD)-inhibitory 5-fluorouracil, is a more potent DPD inhibitor than UFT ; therefore, we hypothesized that postoperative adjuvant chemotherapy with S-1 would be effective for advanced non-small cell lung cancer (NSCLC). We conducted a feasibility study of S-1 as postoperative adjuvant chemotherapy in patients with curatively resected pathological stage II and IIIa NSCLC. **Methods :** Adjuvant chemotherapy consisted of 9 courses (4-week administration, 2-week withdrawal) of S-1 at 80-120 mg/body per day. Twenty-four patients with completely resected NSCLC were enrolled in this study from November 2007 through December 2010. The primary endpoint was the rate of completion of the scheduled adjuvant chemotherapy. The secondary endpoints were safety, overall survival, and relapse-free survival. **Results :** Five patients were censored because of disease recurrence. The planned 9 courses of S-1 were administered to completion in 8 patients. Twelve patients completed more than 70% of the planned courses. Grade 3 adverse reactions, such as elevated total bilirubin (4.2%) and pneumonitis (4.2%), were observed, but there were no Grade 4 adverse reactions. Patients who completed more than 70% of the 9 courses demonstrated better overall survival than those who completed less than 70%. **Conclusion :** Postoperative administration of S-1 may be possible with few severe adverse events as adjuvant chemotherapy for patients with curatively resected pathological stage II-IIIa NSCLC. *J. Med. Invest.* 65 : 90-95, February, 2018

Keywords : Non-small cell lung cancer, S-1, adjuvant chemotherapy, feasibility study.

1. INTRODUCTION

Lung cancer is the most common cause of cancer death worldwide (1). As advanced lung cancer is difficult to cure with surgery alone, even after complete resection, postoperative adjuvant treatments are recommended. It has been reported that patients with completely resected stage I, II, and IIIa non-small cell lung cancer (NSCLC) may benefit from postoperative cisplatin (CDDP)-based chemotherapy (2-5). Although CDDP-based chemotherapy is considered the standard regimen, severe toxicities are occasionally observed and chemotherapy-related death has been one of the problems with adjuvant treatments. As an alternative adjuvant treatment with fewer adverse reactions, oral adjuvant chemotherapy with uracil-tegafur (UFT) has been evaluated. UFT improved the overall survival in patients with completely resected early stage lung adenocarcinoma with only mild adverse reactions in several randomized controlled studies (6, 7).

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral fluoropyrimidine derivative consisting of tegafur (FT), 5-chloro-2,

4-dihydropyridine (CDHP), and potassium oxonate (Oxo), in a molar ratio of 1 : 0.4 : 1 (8). FT is a prodrug of 5-fluorouracil (5-FU) and CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), an enzyme involved in the degradation of 5-FU. The degradation of FT-derived 5-FU is efficiently inhibited by CDHP, and 5-FU remains in the plasma and tumor tissue longer and at higher levels than when low-dose 5-FU is continuously infused intravenously. The major toxicities of fluoropyrimidines are diarrhea and mucositis (9). Oxo is a reversible competitive inhibitor of orotate phosphoribosyltransferase, a phosphoenzyme for 5-FU, and is distributed at high levels in the gastrointestinal tract after oral administration, resulting in a reduction in the gastrointestinal toxicity caused by 5-FU (10).

Considering the points described above, we hypothesized that adjuvant chemotherapy with S-1 would be more effective in postoperative settings than UFT because it is a more potent DPD inhibitor. We conducted a feasibility study of S-1 as postoperative adjuvant chemotherapy in patients with curatively resected pathological stage II and IIIa NSCLC.

Received for publication July 14, 2017 ; accepted January 15, 2018.

Address correspondence and reprint requests to Kazuya Kondo, M.D., Ph.D. Department of Oncological Medical Services, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramotocho, Tokushima City, Tokushima Pref. 770-8503, Japan and Fax : +81-88-633-9031.

2. PATIENTS AND METHODS

2.1. Study design

The present study was designed as a multi-center, single-arm, clinical phase II study to evaluate the feasibility of S-1 adjuvant

therapy in patients with completely resected NSCLC. The primary endpoint was the rate of completing the scheduled adjuvant chemotherapy. The secondary endpoints were safety, overall survival and relapse-free survival. We could not calculate the number of patients to be enrolled in this study based on statistical analysis because this study was an exploratory trial. Twenty-four patients with completely resected NSCLC were enrolled in this study from November 2007 through December 2010. The present study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board at each institution.

2.2. Patient eligibility

Patient eligibility required compliance with the following criteria : (1) histologically proven NSCLC, (2) pathological stage II-IIIa (according to the Union for International Cancer Control 6th edition) after complete resection, (3) no previous treatment except for surgery, (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, (5) age > 20 and < 80 years. Patients also had to have adequate organ function : $3,000 \leq$ leukocytes $\leq 12,000/m^3$, neutrophil count $\geq 1,500/m^3$, thrombocytes $\geq 100,000/m^3$; hemoglobin ≥ 9.0 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $< 2.5 \times$ upper limit of normal (ULN), total bilirubin ≤ 1.5 mg/dL, creatinine ≤ 1.5 mg/dL, creatinine clearance (Ccr) estimated using Cockcroft-Gault's formula ≥ 50 mL/min, and PaO₂ ≥ 60 mmHg. Any patients with a history of drug hypersensitivity, serious surgical or nonsurgical complications, or active secondary cancer were excluded. In addition, pregnant or lactating women were excluded. Written informed consent was obtained from all patients.

2.3. Treatment schedule

Administration of S-1 was started within 2-6 weeks after surgery. The treatment comprised 9 courses (4-week administration, 2-week withdrawal) of S-1 (FT, gimeracil, oteracil potassium; Taiho Pharmaceutical) at 80-120 mg per day according to body surface area (BSA) : BSA < 1.25 m², 80 mg per day ; 1.25 m² \leq BSA < 1.5 m², 100 mg per day ; and 1.5 m² \leq BSA, 120 mg per day. S-1 was administered orally twice daily after meals for 4 weeks, and was thereafter withdrawn for 2 weeks. We checked drug compliance in an interview when patients visited the hospital. Administration of S-1 was temporarily discontinued if a patient had any of the following toxicities : leukocyte count $< 2.0 \times 10^3$ cells/mL, neutrophil count $< 1.0 \times 10^3$ cells/mL, platelet count $< 75 \times 10^3$ cells/mL, total bilirubin $> 1.5 \times$ ULN, ASTs > 150 IU/L, ALTs > 100 IU/L, serum creatinine $> 1.5 \times$ ULN, Ccr < 50 mL/min, or other non-hematological toxicities > 2 . On restarting administration of S-1, the dose was reduced from 120 mg to 100 mg per day, or from 100 mg to 80 mg per day. When treatment was restarted within 7 days, the restart was judged to represent the same course after temporary discontinuation of drug administration. When treatment could not be restarted within 7 days, the course was skipped and restarted as the next course. Treatment was discontinued when the patient exhibited disease recurrence, secondary cancer or adverse reactions that were uncontrollable using dose modification or temporary discontinuation of drug administration. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 3.0.

2.4. Statistical analysis

In the present study, *P*-values and confidence intervals (CI) were double-sided, and *P* < 0.05 was considered to indicate a significant difference. The Kaplan-Meier method was used to estimate the time-to-event functions of overall survival and relapse-free survival. The log-rank test was used to test for possible differences between estimated time-to-event curves. Univariate and

multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. Overall survival was defined as the time from the date of the start of treatment to the date of death or last contact. Relapse-free survival was as the time from the date of the start of treatment to the date of disease progression or death (whichever occurred first) or the date of last contact.

3. RESULTS

3.1 Patient characteristics

Table 1 shows the characteristics of the 24 patients enrolled in the present study. The average age of the patients was 70 years (range, 49-79 years). Thirteen patients were 70 years old or older. Lobectomy or pneumonectomy were performed on all patients.

Table 1. Patient characteristics.

Variables	Number of patients	Percentage
Sex		
Male	16	66.7
Female	8	33.3
Age (years old)		
<60	3	12.5
60-69	8	33.3
70-79	13	54.2
Type of resection		
Lobectomy	21	87.5
Pneumonectomy	3	12.5
Histology		
Adenocarcinoma	19	79.2
Squamous cell carcinoma	4	16.7
Adenosquamous cell carcinoma	1	4.2
TNM stage		
IIA	8	33.3
IIB	6	25.0
IIIA	10	41.7

3.2 Drug compliance

Table 2 shows drug compliance in each course and reasons for the discontinuation of drug administration. The planned 9 courses of S-1 were administered to completion in 8 patients. Five patients were censored because of disease recurrence, and therefore the completion rate was calculated to be 42.1% ; the average number of accomplished courses was 6.3. Twelve patients completed more than 70% of the planned courses. Among these 12 patients, 5 required dose reduction (41.7% of 12 patients). Ten patients discontinued drug administration because of adverse reactions. One patient refused to continue drug administration because of financial problems.

3.3 Adverse events

Table 3 shows a summary of the adverse reactions. Among the adverse reactions, Grade 1 or 2 anorexia (58.3%) was the most frequent, followed by diarrhea (29.2%), and fatigue (25.0%), which were reasons for the discontinuation of drug administration. Although Grade 3 total bilirubin elevation and pneumonitis were

Table 2. Drug compliance (each course) (n=24)

Course	Number of patients entering the course	Percentage	Reasons for discontinuation
1	24	100	
			Grade 2 anorexia (patient refusal)
2	23	95.8	
			Grade 2 anorexia (patient refusal)
			Grade 2 fatigue (patient refusal)
			Recurrence
			Recurrence
3	19	79.2	
			Grade 3 Pneumonitis
			Grade 2 anorexia and weight loss (patient refusal)
			Recurrence
4	16	66.7	
			Grade 1 fatigue (patient refusal)
5	15	62.5	
6	15	62.5	
			Financial problem (patient refusal)
			Grade 2 Vomiting (patient refusal)
			Grade 2 Thrombocytopenia and elevated T-bil (patient refusal)
7	12	50.0	
			Recurrence
			Grade 3 elevated T-bil
8	10	41.7	
			Recurrence
			Grade 2 Weight loss and grade 1 anorexia (patient refusal)
9	8	33.3	

observed in one patient out of 24 patients (4.2%) each, no Grade 4 adverse reactions were noted. There were no treatment-related deaths.

3.4 Survival

Among the 24 patients followed for survival information, 10 had died and 14 were still alive at the time of analysis. The median follow-up time was 70 months (range, 9.5-97.9). At the time of analysis, the median overall survival was 92.4 months (95% CI, 45.5-139.3) (Figure 1). Fourteen patients relapsed, and the median relapse-free survival was 45.5 months (95% CI 16.1-75.0) at the time of analysis (Figure 2). Among 14 patients who relapsed, there were thorax recurrences in 11 patients. There were distant metastases in 3 patients, and metastases of multiple bones, supraclavicular lymph nodes, and adrenal glands were each observed in 1 patient. Except for patients who discontinued treatment because of disease recurrence, overall survival and relapse-free survival were not significantly different between patients who completed the planned 9 courses and those who did not; however, patients who completed more than 70% of the 9 courses exhibited better overall survival than those who completed less than 70% (log-rank test $p=0.038$). In the Cox proportional hazards regression model, completion of more than 70% of the courses was not statistically significant prognosticators for overall survival (Table 4). The relapse-free survival rate also tended to improve in patients who completed more than 70% of the planned courses ($p=0.066$) (Figure 3).

Table 3. Adverse reactions (n=24)

	Grade				Total (Incidence %)
	1	2	3	4	
Laboratory Findings					
Neutropenia	0	1	0	0	4.2
Thrombocytopenia	0	1	0	0	4.2
Elevated AST	6	0	0	0	25.0
Elevated ALT	4	0	0	0	16.7
Elevated T-bil	3	1	1	0	20.8
Gastrointestinal Findings					
Dysgeusia	2	0	0	0	8.3
Anorexia	9	5	0	0	58.3
Nausea	3	1	0	0	16.7
Vomiting	2	0	0	0	8.3
Heartburn	2	0	0	0	8.3
Oral mucositis	3	2	0	0	20.8
Diarrhea	5	2	0	0	29.2
Clinical Findings					
Pigmentation	8	1	0	0	37.5
Dry dermatitis	1	0	0	0	4.2
Itch sensation	1	0	0	0	4.2
Sense of fatigue	5	1	0	0	25.0
Pneumonitis	0	0	1	0	4.2
Weight loss	1	2	0	0	12.5
Dacryorrhea	2	0	0	0	8.3
Vertigo	1	0	0	0	4.2
Nosebleed	1	0	0	0	4.2

Abbreviations : ALT=alanine aminotransferase ; AST= aspartate aminotransferase

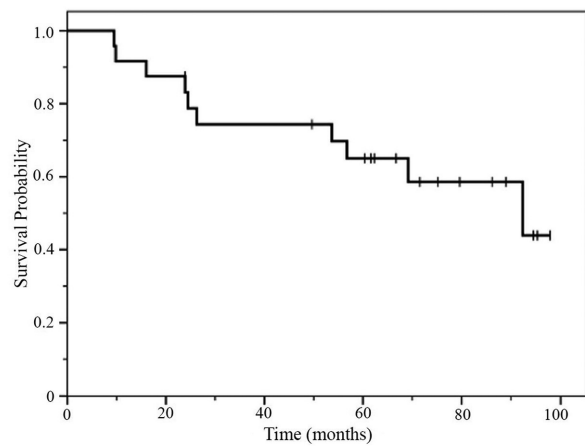


Figure 1. Overall survival of the 24 patients. The median overall survival was 92.4 months (95% CI, 45.5-139.3).

4. DISCUSSION

The present study was carried out to confirm the feasibility of adjuvant chemotherapy with S-1 in patients with curatively resected pathological stage II and IIIA NSCLC. The completion

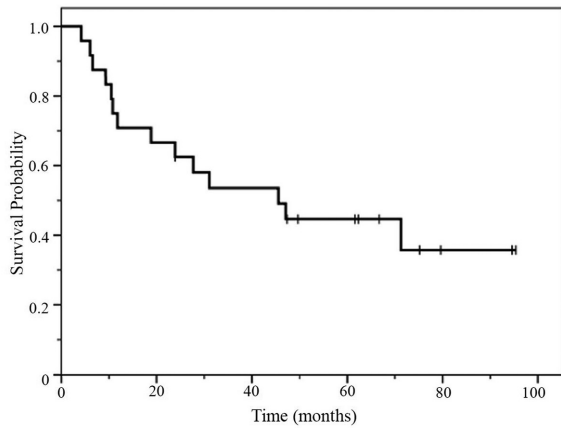


Figure 2. Relapse-free survival among 24 patients. The median relapse-free survival was 45.5 months (95% CI 16.1-75.0).

rate of the scheduled 9 courses of S-1 administration was 42.1%. The completion rate of more than 70% of the scheduled 9 courses was 63.2%. No Grade 4 adverse reactions were observed throughout the 9 courses. Only 2 Grade 3 adverse reactions were encountered (8.3% of total). There were no significant differences in the overall survival rate or the relapse-free survival rate between the treatment completion group and the incompleteness group; however, the overall survival rate was improved in patients who completed more than 70% of the scheduled 9 courses.

Adjuvant chemotherapy after curative surgery with the single-agent S-1 has been proven to improve the overall survival rate in patients with gastric cancer in a randomized phase III trial (11). In that study, adjuvant chemotherapy consisted of 8 cycles (4 weeks of administration and 2 weeks of withdrawal) of S-1 at the same daily dose as that used in the present study (80-120 mg/body) and the completion rate was 65.8%, which was higher than that of the scheduled 9 courses in the present study. In the previous study, the mean age of the patients was 60.3 years and only approximately 30% of the patients were older than 70 years. In the present study, the mean age was 68.1 years and approximately 50% of the patients were older than 70 years. Considering this age difference among the patients in the different studies, the completion rate of the present

Table 4. Cox proportional hazard regression analysis for overall survival

Factor	Univariate			Multivariate		
	Exp(B)	95% confidence interval	P value	Exp(B)	95% confidence interval	P value
Sex Male versus Female	1.684	0.196-14.437	0.635			
Age (years) ≥70 versus <70	8.325	0.937-73.987	0.057	5.646	0.475-67.396	0.170
Histology Adenocarcinoma versus others	1.526	0.178-13.086	0.700			
pStage II versus III	3.223	0.589-17.640	0.177	2.796	0.454-17.230	0.268
Completion rate (%) ≥70 versus <70	0.140	0.016-1.212	0.074	0.420	0.031-5.645	0.513

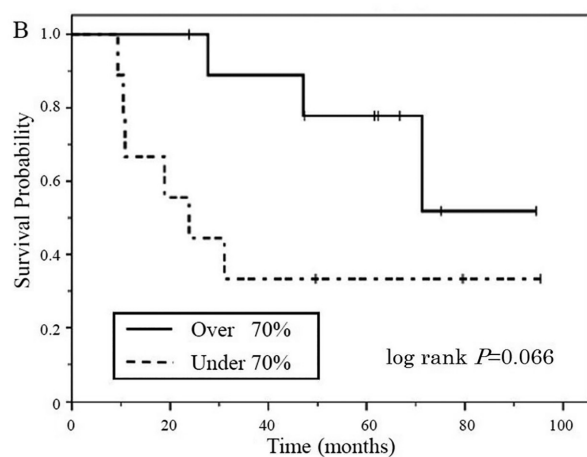
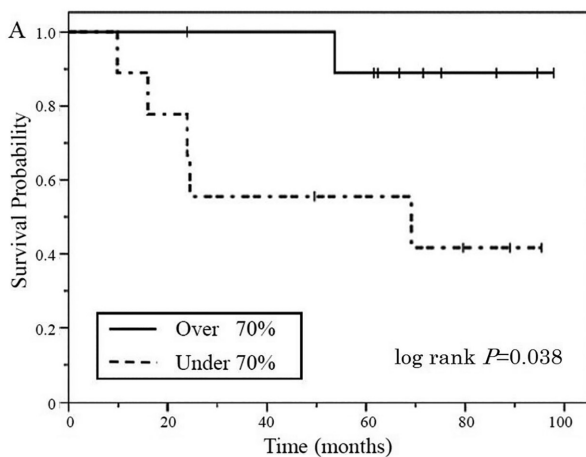


Figure 3. Overall survival (OS) (A) and relapse-free-survival (RFS) rates (B).

Except for the patients who discontinued treatment because of disease recurrence, in the over 70% of completed courses group, OS was improved and the RFS rate also tended to improve compared with the under 70% completed courses group.

study was acceptable.

There were few severe adverse events in the present study. Currently, the standard regimen for adjuvant chemotherapy in postoperative patients with stage II-IIIa NSCLC is cisplatin doublet. The LACE Collaborative Group published a meta-analysis of the 5 largest randomized cisplatin-based trials (5). The LACE meta-analysis demonstrated that both overall survival and disease-free survival were improved with the administration of cisplatin. However, there was a significant interaction between chemotherapy effects and World Health Organization (WHO) performance status (PS). In the 5 trials, the rate of overall Grade 3 to 4 toxicity was 66%. It is difficult for patients with a poor PS to receive cisplatin-based chemotherapy because of this high level of toxicity. In the present study, the rate of Grade 3 toxicity was 8.3% and there were no Grade 4 toxicities. Adjuvant chemotherapy with S-1 was performed with few severe adverse events. The most common adverse events were Grade 1 or 2 anorexia (54.2%), which was the reason for discontinuation of S-1 administration. Gastrointestinal toxicities, such as oral mucositis and diarrhea, were also frequent; thus, the completion rate may improve with supportive therapies for gastrointestinal toxicity and with a frequent withdrawal schedule of S-1.

There was a significant benefit for the overall survival rate in patients who completed more than 70% of the scheduled 9 courses. Although there were no significant differences, the relapse-free survival rate tended to improve in patients who completed more than 70% of the scheduled 9 courses. In the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) (11), a randomized phase III study of chemotherapy with S-1 after curative surgery in Japanese patients with locally advanced gastric cancer, the overall survival rate and the relapse-free survival rate in the S-1 group at 5 years were better than in the surgery-only group. In the same study, patients who completed more than 70% of the planned courses exhibited better overall survival than those who completed less than 70%. The same trend was seen in our present study. Based on ACTS-GC data, adjuvant chemotherapy with S-1 after curative resection of advanced gastric cancer is considered the standard regimen. In NSCLC, some feasibility studies of postoperative chemotherapy with S-1 have reported, but there has not been a randomized study to confirm the effectiveness of postoperative adjuvant chemotherapy with S-1. Some phase II study of adjuvant chemotherapy with S-1 (12-16) have been reported (Table 5). In these studies, the treatment comprised 8 courses of S-1 at 80-120 mg per day. When comparing the 4-week administration and 2-week withdrawal setting group with the 2-week administration and 1-week withdrawal setting group, there was no difference in the completion rate between the 2 groups. However, a high incidence of Grade 3 or 4 adverse events was observed in the 4-week administration and 2-week withdrawal setting group. We planned the treatment schedule as 4-week administration, 2-week with-

drawal of S-1 in our present study. There was no difference in the incidence of severe adverse events; however, the completion rate was low. In the feasibility trial for adjuvant chemotherapy with docetaxel plus cisplatin followed by long term administration of S-1 (14), Grade 3 or 4 neutropenia was observed in 78.5% of patients during the DOC + CDDP treatment. In contrast, Grade 3 or 4 adverse events were seen in 1.8-7.3% of patients during the S-1 treatment. Iwamoto *et al.* reported a randomized study of adjuvant chemotherapy with S-1 versus cisplatin + S-1 in completely resected advanced NSCLC (17). The incidence of adverse events was significantly lower among the patients in the S-1 group, and there was no significant difference in the overall survival rate and relapse-free survival rate. The results showed that adjuvant therapy with S-1 could be effective without severe adverse effects.

Kato *et al.* (6) reported that adjuvant chemotherapy with UFT with the same DPD inhibitor activity as fluoropyrimidine S-1 improved survival among patients with completely resected stage I lung adenocarcinoma in a randomized trial. Based on these results, S-1 can be effective as adjuvant chemotherapy in surgically removed progressive lung cancer because of more potent DPD inhibition than UFT. 5-FU was previously thought to be inappropriate for lung cancer treatment because the lung contains higher levels of DPD than other organs, such as the stomach and colon (13). However, it was reported that lung adenocarcinoma had higher DPD expression than squamous cell carcinoma, especially adenocarcinoma in situ (14). Therefore, S-1 may be more effective in adjuvant therapy for advanced lung cancer than for gastric cancer.

There are some limitations in this study. First, the number of patients in this study is not enough to draw definitive conclusions from the prognostic analysis. Second, we checked drug compliance in an interview, and had no way of verifying whether the patients were truthful about drug compliance because S-1 therapy was performed as an ambulatory treatment.

In conclusion, postoperative administration of S-1 may be possible with few severe adverse events as adjuvant chemotherapy for patients with curatively resected pathological stage II-IIIa NSCLC. S-1 can be administered orally with few toxicities; therefore, it is expected to be a promising agent for adjuvant chemotherapy in advanced lung cancer. Based on this feasibility study, a randomized trial to evaluate the efficacy of S-1 as adjuvant chemotherapy with low toxicity for resected advanced NSCLC is required in the future.

CONFLICT OF INTEREST

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Table 5. Selected phase II clinical trials of adjuvant chemotherapy with S-1 for completely resected NSCLC.

Trial	Drug	Dose/ schedule				Planned courses	No. of pts.	Completion rate	Adverse events (Grade 3, 4)
		Per day	On days	Duration					
Yano (2010) ¹²	S-1	80-120 mg	1-14	q3wks	8	30	56.7%	6.7%	
Tsuchiya (2012) ¹³	S-1	80-120 mg	1-28	q6wks	8	50	72%	2%-4%	
Niho (2013) ¹⁴	DOC+CDDP followed by S-1	60 mg/m ²	Day 1	q3-4wks	3	129	51.2%	78.5% (DOC+CDDP) 1.8-7.3% (S-1)	
		80 mg/m ²	Day 1	q3-4wks	3				
		40 mg/m ²	1-14	q3wks	6-12 months				
Okumura (2013) ¹⁵	S-1	80 mg/m ²	1-28	q6wks	8	28	50%	14.2%	
Maruyama (2014) ¹⁶	S-1	50-100 mg	1-14	q3wks	8	25	50%	4%	

REFERENCES

1. Rebecca Siegel, Deepa Naishadham, Ahmedin Jemal : Cancer statistics. *CA Cancer J Clin* 63 : 11-30, 2013
2. Arriagada R, Bergman B, Dunant A, *et al* : Cisplatin-based adjuvant chemotherapy for completely resected non-small-cell-lung cancer. *N Engl J Med* 350 : 351-360, 2004
3. Winton T, Livingston R, Johnson D, *et al* : Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 352 : 2589-2597, 2005
4. Douillard JY, Rosell R, De Lena M, *et al* : Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]) : a randomised controlled trial. *Lancet Oncol* 7 : 719-727, 2006
5. Pignon JP, Tribodet H, Scagliotti GV, *et al* : Lung adjuvant cisplatin evaluation : a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 26 : 3552-3559, 2008
6. Kato H, Ichinose Y, Ohta M, *et al* : A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 350 : 1713-1721, 2004
7. Hamada C, Tsuboi M, Ohta M, *et al* : Effect of postoperative adjuvant chemotherapy with tegafur-uracil on survival in patients with stage IA non-small cell lung cancer : an exploratory analysis from a meta-analysis of six randomized controlled trials. *J Thorac Oncol* 4 : 1511-1516, 2009
8. Shirasaka T, Nakano K, Takechi T, *et al* : Antitumor activity of 1 M tegafur-0.4 M 5-chloro-2, 4-dihydropyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res* 56 : 2602-2606, 1996
9. Vogelzang NJ : Continuous infusion chemotherapy : a critical review. *J Clin Oncol* 2 : 1289-1304, 1984
10. Shirasaka T, Shimosato Y, Fukushima M : Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 53 : 4004-4009, 1993
11. Sakuramoto S, Sasako M, Yamaguchi T, *et al* : Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 357 : 1810-1820, 2007
12. Yano T, Yamazaki K, Maruyama R, *et al* : Feasibility study of postoperative adjuvant chemotherapy with S-1 (tegafur, gimeracil, oteracil potassium) for non-small cell lung cancer-LOGIK 0601 study. *Lung Cancer* 67 : 184-187, 2010
13. Tsuchiya T, Nagayasu T, Yamasaki N, *et al* : A multicenter phase II study of adjuvant chemotherapy with oral fluoropyrimidine S-1 for non-small-cell lung cancer : high completion and survival rates. *Clin Lung Cancer* 13 : 464-469, 2012
14. Niho S, Ikeda N, Michimae H, *et al* : Feasibility trial for adjuvant chemotherapy with docetaxel plus cisplatin followed by single agent long-term administration of S-1 chemotherapy in patients with completely resected non-small cell lung cancer : Thoracic Oncology Research Group Study 0809. *Br J Cancer* 109 : 545-551, 2013
15. Okumura S, Sasaki T, Satoh K, *et al* : Feasibility of adjuvant chemotherapy with S-1 consisting of a 4-week administration and a two-week rest period in patients with completely resected non-small cell lung cancer. *Mol Clin Oncol* 1 : 124-130, 2013
16. Maruyama R, Ebi N, Kishimoto J, *et al* : A feasibility trial of postoperative adjuvant chemotherapy with S-1, an oral fluoropyrimidine, for elderly patients with non-small cell lung cancer : a report of the Lung Oncology Group in Kyushu (LOGIK) protocol 0901. *Int J Clin Oncol* 19 : 57-62, 2014
17. Iwamoto Y, Mitsudomi T, Sakai K, *et al* : Randomized Phase II Study of Adjuvant Chemotherapy with Long-term S-1 versus Cisplatin+S-1 in Completely Resected Stage II-IIIa Non-Small Cell Lung Cancer. *Clin Cancer Res* 21 : 5245-5252, 2017
18. Nishimura M, Naito S : Tissue-specific mRNA expression profiles of human phase I metabolizing enzymes except for cytochrome P450 and phase II metabolizing enzymes. *Drug Metab Pharmacokinet* 21 : 357-374, 2006
19. Mochinaga K, Tsuchiya T, Nagasaki T, *et al* : High expression of dihydropyrimidine dehydrogenase in lung adenocarcinoma is associated with mutations in epidermal growth factor receptor : implications for the treatment of non-small-cell lung cancer using 5-fluorouracil. *Clin Lung Cancer* 15 : 136-144.e4, 2014