Original Article

Randomized feasibility study of S-1 for adjuvant chemotherapy in completely resected Stage IA non–small-cell lung cancer: results of the Setouchi Lung Cancer Group Study 0701

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Abstract

Objective: The aim of this multicenter study was to determine the appropriate administration schedule for S-1, an oral fluoropyrimidine, for adjuvant chemotherapy in patients with completely resected pathological-Stage IA (tumor diameter, 2–3 cm) non–small-cell lung cancer.
Methods: Patients were randomly assigned to receive adjuvant chemotherapy consisting of either the 4-week oral administration of S-1 (80–120 mg/body/day) followed by a 2-week rest (Group A), or the 2-week oral administration of S-1 (80–120 mg/body/day) followed by a 1-week rest (Group B). The duration of adjuvant chemotherapy was 1 year in both arms. The primary endpoint was compliance, namely drug discontinuation-free survival, which was calculated using the Kaplan–Meier method with log-rank test.
Results: Eighty patients were enrolled in this study, and 76 patients actually received S-1 treatment. The drug discontinuation-free survival rates at 1 year were 49.1% in Group A and 52.7% in

Group B (*P* = 0.373). The means of the relative dose intensities were 55.3% in Group A and 64.6% in Group B (*P* = 0.237). There were no treatment-related deaths. Patients with grade 3/4 toxicities were significantly more frequent in Group A (40.5%) than in Group B (15.4%, *P* = 0.021). The 2-year relapse-free survival rates were 97.5% in Group A and 92.5% in Group B, and the 2-year overall survival rates were 100% in both groups.

Conclusions: The feasibility showed no significant difference between the two groups among patients with completely resected Stage IA (tumor diameter, 2–3 cm) non–small-cell lung cancer.

Key words: clinical trials, non–small-cell lung cancer, adjuvant chemotherapy, S-1

Introduction

Lung cancer is a leading cause of cancer-related death in the world (1). Whereas surgery is considered to be the primary treatment modality for early stage non–small-cell lung cancer (NSCLC), the 5-year overall survival (OS) rates are 85.9% and 69.3% for pathological-Stage IA and IB NSCLC patients, respectively (2), and 15% of patients with Stage IA NSCLC develop distant recurrences even after radical resection (3). As for adjuvant chemotherapies for completely resected NSCLC, several randomized Phase III trials and meta-analyses have revealed that adjuvant chemotherapy with uracil-tegafur (UFT) can reduce the risk of relapse and death from lung cancer following surgical resection in Japanese patients with Stage I adenocarcinoma, especially for pathological-Stage IA with a tumor size >2 cm and pathological-Stage IB (4–8). Based on these findings, the Japanese Lung Cancer Practice Guidelines, which were developed by the Japanese Society of Lung Cancer (9), recommends the administration of UFT for the patients with completely resected pathological-Stage I (pT1 >2 cm and pT2) NSCLC (Grade B recommendation) (10) (http://www.haigan.gr.jp/modules/guideline/index.php?content_id=3).

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral fluorouracil antitumor drug that consist of tegafur (a prodrug of 5-fluorouracil [5-FU]), gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil) and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 (11), while UFT consists of tegafur and uracil at a molar ratio of 1:4. After the approval of UFT, S-1 was developed to improve the tumor-selective cytotoxicity of 5-FU and UFT, and it was approved in Japan for the treatment of gastric cancer in 1999 and NSCLC in 2004, respectively.

The original administration schedule for S-1 is 4 weeks administration followed by a 2-week rest period for 1 year (conventional schedule) and the feasibility of administration of S-1 according to this conventional schedule has been previously confirmed in patients with completely resected NSCLC (12,13). However, the discontinuation or dose reduction of S-1 administration is often observed because of adverse events during the conventional schedule of treatment.

To decrease the toxicity of S-1 and to maintain the efficacy of S-1, a modified schedule, in which S-1 is administered for 2 weeks followed by a 1-week rest period (modified schedule), is clinically used if patients receiving treatment according to the conventional schedule experience severe toxicities (14,15). A randomized scheduling feasibility study for S-1 showed that the modified schedule seemed to be more feasible than the conventional schedule for patients with locoregionally advanced squamous cell carcinoma of the head and neck (16). Several clinical feasibility studies of S-1 as an adjuvant therapy have already been performed in NSCLC patients with pathological-Stage IB–IIIB (13,17) or with pathological-Stage IB-IIIA (12,15). However, the feasibility of S-1 administration schedules (conventional versus modified schedule) has not been examined in completely resected NSCLC patients as a randomized clinical trial.

In this study, we conducted a randomized feasibility study comparing the conventional schedule of S-1 administration and the modified schedule to determine the appropriate treatment schedule for S-1 adjuvant chemotherapy in patients with completely resected pathological-Stage IA (tumor diameter, 2–3 cm) NSCLC.

Patients and methods

Patients

Patients who met all the following eligibility criteria and none of the following exclusion criteria were enrolled in this study. The eligibility criteria were as follows: (i) completely resected NSCLC, pathological-Stage IA (according to the Union Internationale Countre le Cancer seventh TNM edition) (18) with a tumor diameter of 2–3 cm, (ii) within 4–6 weeks after a surgical resection that lobectomy or more extensive resection of the lung, with complete lymph node dissection (ND2a or more extensive dissection in principle); (iii) no prior chemotherapy or radiotherapy; (iv) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (v) adequate organ function (leukocytes ≥ 3000/μL and ≤ 12000/μL; neutrophils ≥ 1500/μL; platelets ≥ 100 000/μL; hemoglobin ≥ 9.0 g/dL; total bilirubin ≤ 1.5 mg/dL; aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2.5 x upper limit of normal [ULN]; serum creatinine ≤ 1.5 mg/dL or creatinine clearance ≥ 60 mL/min; PaO$_2$ ≥ 60 mmHg) and (vi) written informed consent. The exclusion criteria were as follows: (i) serious infectious disease, uncontrolled diabetes mellitus and hypertension, and other diseases interfering with S-1 treatment; (ii) acute myocardial infarction or unstable angina pectoris within 6 months; (iii) interstitial pneumonia or obvious interstitial shadow on chest X-ray; (iv) systemic administration of a steroid; (v) active concomitant malignancy; (vi) pregnancy or lactation; (vii) psychiatric disease; (viii) administration of other pyrimidine fluoride drugs; (ix) administration of phenytoin and warfarin and (x) other inadequate conditions, as judged by the attending physician.

All the patients provided written informed consent prior to enrollment in the study.

Treatment plan and follow-up

The randomization was performed centrally at the Division of Molecular Medicine, Aichi Cancer Center Research Institute, Aichi, Japan, with the following stratification factors: institute, histology (adenocarcinoma versus others) and surgical procedure (lobectomy

versus others). Patients received S-1 orally twice daily; the dose was 80 mg/body/day when the body surface area was <1.25 m^2, 100 mg/body/day for 1.25–1.50 m^2 and 120 mg/body/day for >1.50 m^2. S-1 was randomly administered for 4 weeks followed by a 2-week rest period (Group A) or 2 weeks followed by a 1-week rest period (Group B). These cycles were repeated every 6 weeks (Group A) or 3 weeks (Group B) until 1 year after the start of oral administration.

The oral administration of S-1 was paused if any of the following toxicities were observed during the course of treatment: leukocytes < 1000/μL, neutrophils < 500/μL, platelets < 50 000/μL, hemoglobin < 8.0 g/dL, ASTs and ALTs > 2.5 x ULN; serum bilirubin > 1.5 mg/dL; serum creatinine > 1.5 mg/dL; febrile neutropenia or other non-hematological toxicities ≥ grade 3.

The oral administration of S-1 was started if all of the following criteria were fulfilled on Day 1 of each treatment course: leukocytes ≥ 3000/μL, neutrophils ≥ 1500/μL, platelets ≥ 100 000/μL, hemoglobin ≥ 9.0 g/dL, ASTs and ALTs ≤ 2.5 x ULN; serum bilirubin ≤ 1.5 mg/dL; serum creatinine ≤ 1.5 mg/dL or other non-hematological toxicities except for depilation ≤ grade 1.

The S-1 dose was reduced from 120 to 100 mg, from 100 to 80 mg or from 80 to 50 mg in the next cycle if the patients had suffered from any of the following toxicities: >4 days of a continuously low leukocyte level (<1000/μL) or a low neutrophil level (<500/μL) even after granulocyte-colony stimulating factor administration; a platelet level < 25 000/μL or the need for a platelet transfusion; ASTs and ALTs > 2.5 x ULN; a serum bilirubin level > 1.5 mg/dL; a serum creatinine level > 1.5 mg/dL or other non-hematological toxicities ≥ grade 3. Dose reduction was permitted twice during whole course from 120 to 100 mg, 100 to 80 mg, 80 to 50 mg or 50 to 40 mg in the next cycle.

Patients received S-1 administration unless they had experienced a relapse or any of the following discontinuation criteria were present: (i) severe toxicities or complications, (ii) the next cycle was delayed because of toxicities until more than Day 58 in Group A or Day 44 in Group B, (iii) patient's refusal or (iv) other inadequate conditions, as judged by the attending physician.

For the baseline evaluations, the results of a medical history and physical examination, the operation date, the pathological-TNM status, the tumor histology, any comorbidities and the results of laboratory analyses were noted. During S-1 treatment, a physical examination, ECOG PS, chest X-ray, blood counts and biochemical examinations were performed at least once every 3 weeks. After S-1 treatment and until 3 years after the initiation of the protocol treatment, the patient evaluations mentioned above were performed every month and a chest CT scan was performed at least once every 6 months. From 3 to 5 years after the initiation of the protocol treatment, the same patient evaluations were performed every 3 months and a chest CT scan was performed at least once every 12 months. Toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

Statistical analysis

This study was designed as a multicenter feasibility study, and the study protocol was approved by the institutional review board of each participating institution (the UMIN Clinical Trial Registry as UMIN000006967). The primary endpoint of this study was compliance. Compliance, namely drug discontinuation-free survival, was defined to determine the appropriate treatment schedule at 1 year using the Kaplan–Meier method with log-rank test. Patients who discontinued the protocol treatment because of tumor recurrence or

other complications unrelated to S-1 administration were treated as censored cases. The total number of S-1 administration days and the relative dose intensity (RDI) of S-1, which was defined as the ratio between the actual total administration dose per whole treatment period including drug holiday and the planned total administration dose per whole treatment period including drug holiday, were also calculated.

Sample size was estimated by using a selection problem approach [19] with 90% probability of selecting correct arm. We assumed a 1-year compliance rate of 50% and 65% for Groups A and B, respectively, based on the previous report [16]. According to these, we estimated required number of patients as 36 patients in each arm. Finally, sample size was set as 80 considering potential drop-out of patients due to ineligibility.

The secondary endpoints were toxicity, relapse-free survival (RFS) and OS. A final analysis of survival time will be performed 5 years after the last enrollment.

Significant differences among categorized groups were compared using Fisher's exact test or the Mann–Whitney test. A univariate analysis of OS and RFS was performed using the Kaplan–Meier method with log-rank test. We defined $P < 0.05$ as a threshold of statistical significance. All the statistical analyses were executed using STATA ver11 (College Station, TX, USA) and GraphPad Prism 5 (La Jolla, CA, USA).

Results

Patient characteristics

Eighty patients were enrolled in this trial from 11 institutions in Japan between October 2007 and December 2012. Four patients refused the protocol treatment before starting therapy, and 76 patients were therefore eligible (37 in Group A and 39 in Group B). The baseline characteristics of the eligible patients are summarized in Table 1. Forty-six patients (60.5%) were men, and the median age was 64 years old. Adenocarcinoma was the major histology appearing in 64 (84.2%) patients.

Compliance and feasibility

During the 1-year treatment course, oral administration was continued for 252 days without drug withdrawal in both groups. Overall, 8.1% of the patients in Group A and 10.2% of the patients in Group B received S-1 administration according to the planned schedule (total of 252 days) and completed the initial dose without requiring a dose reduction (difference not significant) (Table 2). Administration was stopped because of adverse events in 19 (51.4%) patients and 18 (46.2%) patients in Groups A and B, respectively, and dose reduction was needed in 11 (29.7%) patients and 12 (30.8%) patients in Groups A and B, respectively (Table 2). In order to complete a last treatment course, 12 patients (5 and 7 patients in Groups A and B, respectively) continued the treatment for >365 days based on physicians' discretion (median 371 days, range 366–386) (Fig. 1).

The drug discontinuation-free survival rates at 1 year after the onset of drug administration were 49.1% (95% confidential interval [95% CI]: 31.9–64.2%) for Group A and 52.7% (95%CI: 35.6–67.2%) for Group B, respectively ($P = 0.373$, Fig. 1 and Table 3). There were four censor cases who discontinued S-1 administration because of tumor recurrence ($n = 1$) or appearance of other disease unrelated to S-1 administration (one case of secondary primary NSCLC, one of gastric polyp and one of testis tumor). We also evaluated the drug discontinuation-free survival rates at 1 year

Table 1. Characteristics of 76 eligible patients

Subsets			Total (n = 76)	Group A (n = 37)	Group B (n = 39)	P
Age	Median (range)		64 (40–84)	63 (40–84)	64 (49–76)	0.502
Sex	Male		46	22	24	0.853
	Female		30	15	15	
Smoking	Never		31	16	15	0.599
	Ever	All	45	21	24	
		Current	16	6	10	
		Former	29	15	14	
Histology	Ad		64	31	33	1.000
	Sq		8	4	4	(Ad vs. others)
	Adsq		1	1	0	
	Large		1	0	1	
	Pleomorphic		2	1	1	
Tumor site	RUL		32	12	20	0.163
	RML		2	2	0	
	RLL		21	12	9	
	LUL		12	5	7	
	LLL		9	6	3	

Group A, 4-week administration of S-1 followed by a 2-week rest; Group B, 2-week administration of S-1 followed by a 1-week rest; Ad, adenocarcinoma; Sq, squamous cell carcinoma; Adsq, adenosquamous cell carcinoma; Large, large cell carcinoma; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 2. S-1 administration

	Group A (n = 37)		Group B (n = 39)	
	n	%	n	%
Patients following planned schedule and dose[a]	3	8.1	4	10.2
Patients who completed oral administration without dose reduction for less than 252 days	4	10.8	5	12.8
Patients in whom administration was stopped due to adverse events	19	51.4	18	46.2
Patients with dose reduction	11	29.7	12	30.8

[a]Patients who completed oral administration without drug withdrawal and dose reduction for 252 days.

Figure 1. Drug discontinuation-free survival curve. The drug discontinuation-free survival curves after onset of drug are shown using the Kaplan–Meier method. The curves are drawn until 365 days after onset of drug although 12 patients took S-1 for >365 days in order to complete a last treatment course based on physicians' discretion. Group A, 4-week oral administration of S-1 followed by a 2-week rest; Group B, 2-week oral administration of S-1 followed by a 1-week rest.

considering these four cases as event cases, and found that the drug discontinuation-free survival rates were 46.0% (95%CI: 29.6–60.9%) for Group A and 47.8% (95%CI: 31.3–62.6%) for Group B, respectively ($P = 0.360$). The mean of total administration days was 219.9 days (standard deviation [SD], 148.0 days) in Group A and 263.4 days (SD, 121.6 days) in Group B, respectively (Table 3). The means of the RDI were 55.3% (SD, 35.2%) in Group A and 64.6% (SD, 33.1%) in Group B, respectively (Table 3).

Toxicity

A summary of the adverse events is shown in Table 4. The main adverse events were hematological, gastrointestinal and cutaneous symptoms. Drug-related adverse events were recorded for all the patients (100%) in both groups. Severe adverse events (grade 3 or 4) was significantly more frequent in Group A (40.5%) than in Group B (15.4%, $P = 0.021$; Table 4). Two patients showed grade 4 adverse events (one each in each group), but no treatment-related deaths occurred during the protocol treatment. As for mild adverse
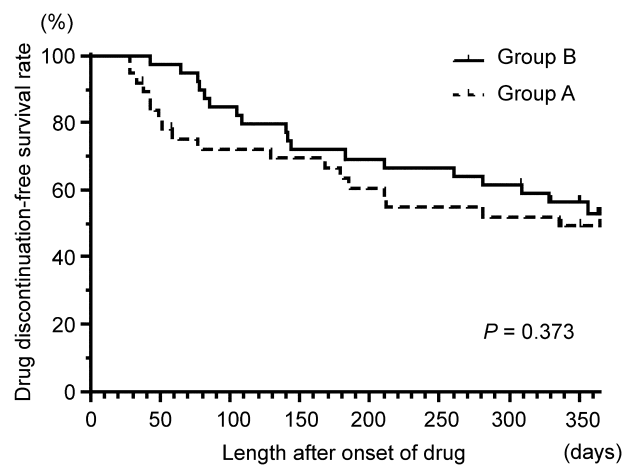
event (grade 1 or 2), an elevated serum AST or ALT level and keratitis/conjunctivitis were significantly more frequent in Group B (66.7% and 43.6%, respectively) than in Group A (24.3% and 13.5%, respectively) ($P = 0.0003$ and 0.0052, respectively).

Survival

The median follow-up times were both 28 months, at which point all eligible patients ($n = 76$) and all the enrolled patients ($n = 80$) had been followed up for at least 2 years. Survival analyses were performed based on an intention to treat. The 2-year RFS rates for all patients ($n = 80$) were 97.5% in Group A and 92.5% in Group B,

respectively. The 2-year OS rates for all patients ($n = 80$) were both 100% in both groups.

Discussion

Previous single arm Phase II studies of S-1 adjuvant chemotherapy for Stage IB-IIIA NSCLC patients revealed that the treatment completion rate of S-1 at 1 year of administration were 50–72% [12,13]. The drug discontinuation-free survival rates at 1 year of this study were similar to these previous reports, suggesting that both schedules of S-1 administration in this study are acceptable.

Two randomized feasibility studies of S-1 as an adjuvant chemotherapy have been performed comparing a 4-week S-1 administration schedule followed by a 2-week rest and a 2-week S-1 administration schedule followed by a 1-week rest in patients with gastric [20] or head and neck [16] cancer. These studies revealed that the completion rate for the 2-week administration schedule was >15% higher than that for the 4-week administration schedule; 89% versus 49%, respectively ($P = 0.0046$) [20] and 69.4% versus 54.4%, respectively ($P = 0.15$) [16]. We assumed the 1-year compliance rate of 50% and 65% for Groups A and B, respectively, but our study found that there were no significant differences between two groups although Group B

Table 3. Compliance of S-1 administration

	Group A ($n = 37$)	Group B ($n = 39$)	P
Drug discontinuation-free survival rate at 1 year after drug onset (95% CI)	49.1% (31.9–64.2)	52.7% (35.6–67.2)	0.373
Total treatment period (days)			
Mean	219.9 days	263.4 days	0.165
Standard deviation	148.0 days	121.6 days	
Relative dose intensity at 1 year			
Mean	55.3%	64.6%	0.237
Standard deviation	35.2%	33.1%	

showed a slightly higher drug discontinuation-free survival rate at 1 year, total treatment period and mean RDI. These differences according to the types of primary disease and surgery may depend on the difference in the pharmacokinetics of S-1, such as after a gastrectomy in gastric cancer patients [21].

As for toxicity, we found that severe grade 3/4 toxicities were significantly more frequent in Group A than in Group B as previously described by Tsukuda et al. [16], suggesting that the schedule used in Group B may be more tolerable than that used in Group A.

Cisplatin (CDDP)-based chemotherapies are recommended for patients with surgically resected pathological-Stage II and IIIA NSCLC patients [22,23]. However, the regimens and indications for adjuvant chemotherapy are controversial for pathological-Stage I NSCLC patients. As for pathological-Stage IB NSCLC, the NCCN guidelines (download date, 19 January 2016) recommended CDDP-based chemotherapies or observation (www.nccn.org/professionals/physician_gls/pdf/nscl.pdf), but as mentioned above, the Japanese Society of Lung Cancer [9] recommended the oral administration of UFT for pathological-Stage IB NSCLC and pathological-Stage IA in patients with pT1b NSCLC based on a randomized phase III study [5] and a meta-analysis of five clinical trials [6,7]. Although both UFT and S-1 have been approved as adjuvant chemotherapies for completely resected NSCLC patients, S-1 showed several advantages when compared with UFT. Using a rat orthotopical xenograft model of human colon carcinomas, S-1 showed a significantly higher tumor growth inhibition and a significantly prolonged survival period than UFT [11]. S-1 administration (15 mg/kg) also produced a higher 5-FU level in the plasma, a higher rate of 5-FU incorporation into the RNA in the tumor, and a higher thymidylate synthase inhibition rate in the tumor, compared with UFT administration (30 mg/kg) [11].

The incidence of severe adverse events associated with the daily administration of UFT for 2 years (0.9–2.1%) [5,24,25] has been reported to be lower than that for the 4-week administration of S-1 followed by a 2-week rest for 1 year (12–14%) [12,13] in resected NSCLC patients. To evaluate the efficacy of S-1 as compared with UFT, the Japan Clinical Oncology Group (JCOG) conducted a randomized phase III study to evaluate the 2-week administration of S-1 followed by a 1-week rest for 1 year compared with the daily

Table 4. Adverse event

Adverse event	Group A ($n = 37$)		Group B ($n = 39$)		P	
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Any adverse events	22 (59.5%)	15 (40.5%)	33 (84.6%)	6 (15.4%)	0.021	0.021
Leukopenia	8 (21.6%)	2 (5.4%)	13 (33.3%)	0	0.310	0.234
Neutropenia	12 (32.4%)	3 (8.1%)	15 (38.5%)	0	0.637	0.111
Thrombocytopenia	12 (32.4%)	0	18 (46.2%)	2 (5.1%)	0.248	0.494
Elevation of bilirubin	19 (51.4%)	0	17 (43.6%)	1 (2.6%)	0.646	1.000
Elevation of ALT/AST	9 (24.3%)	2 (5.4%)	26 (66.7%)	0	0.0003	0.234
Anorexia	14 (37.8%)	1 (2.7%)	23 (59.0%)	0	0.072	0.487
Nausea and vomiting	3 (8.1%)	2 (5.4%)	4 (10.3%)	0	1.000	0.234
Diarrhea	18 (48.6%)	4 (10.8%)	12 (30.8%)	1 (2.6%)	0.159	0.194
Stomatitis	9 (24.3%)	0	8 (20.5%)	2 (5.1%)	0.786	0.494
Cutaneous symptoms	5 (13.5%)	3 (8.1%)	5 (12.8%)	0	1.000	0.111
Keratitis/conjunctivitis	5 (13.5%)	1 (2.7%)	17 (43.6%)	1 (2.6%)	0.0052	1.000
General fatigue	2 (5.4%)	1 (2.7%)	0	0	0.234	0.487
Pneumonia	9 (24.3%)	1 (2.7%)	10 (25.6%)	1 (2.6%)	1.000	1.000

G1/2, adverse event of grade 1 or 2; G3/4, adverse event of grade 3 or 4; any adverse events indicate the number of patient who suffered from any of adverse events; underlined *P* values indicate statistically significant ($P < 0.05$). ALT, alanine aminotransferase; AST, aspartate aminotransferase.

administration of UFT for 2 years for pathological-Stage I (tumor diameter >2 cm) NSCLC patients; patient accrual for this study has been completed (JCOG0707, UMIN000001494). This JCOG0707 study is originally a superiority trial for S-1 treatment compared with UFT treatment and the primary endpoint was OS. However, the results of interim analysis indicated that primary endpoint should be modified to RFS due to less death events than expected. In case of S-1 treatment does not showed significant advantage for primary endpoint, the treatment schedule of S-1 should be modified to the regimen.

To reduce the adverse effects and maintain a prolonged antitumor effect of constitutive S-1 administration, an alternative-day S-1 administration schedule has recently been attempted. The cell cycle period of normal cells is shorter than that of tumor cells (0.5–1.5 days versus 5–7 days, respectively) (26,27). In tumor cells, 5-FU can exert an antitumor effect during S-phase even though 5-FU is being administered every other day, while normal cells can avoid daily exposure to 5-FU, thereby reducing the frequency of adverse events especially in gastrointestinal cells and bone marrow (28,29). Based on this concept, several clinical trials examining alternative-day S-1 administration have been conducted for some malignancies, such as gastric (30,31), pancreatic (32) and head and neck cancers (33). As for NSCLC, our study group (UMIN000011994 and UMIN000007819) and another group (UMIN000006981) are now conducting randomized Phase II trials to confirm the advantage of alternative-day S-1 administration compared with constitutive S-1 administration.

A limitation of this study is its insufficient follow-up period. Although the 2-year OS and RFS rates, which were equivalent or superior to those of a previous study (2), were similar between both groups, the long-term effects of these schedules on survival may differ between the two groups.

In conclusion, the feasibility of the S-1 administration schedules used in Groups A and B showed no significant difference for adjuvant chemotherapy of patients with completely resected pathological-Stage IA (tumor diameter, 2–3 cm) NSCLC.

Acknowledgements

Conflict of interest statement

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