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S-1 vs. paclitaxel plus carboplatin as adjuvant chemotherapy for completely resected stage II/IIIA non-small-cell lung cancer

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Abstract. The majority of patients with completely resected stage II or IIIA non-small-cell lung cancer (NSCLC) require adjuvant chemotherapy to improve survival following surgery. In the present trial, the 2-year disease-free survival (DFS), and the feasibility and safety of S-1 as an adjuvant chemotherapy for advanced lung cancer were evaluated. A total of 40 patients with completely resected stage II or IIIA NSCLC were enrolled and randomized to receive postoperative chemotherapy with either up to 4 cycles of paclitaxel plus carboplatin (arm A) or with up to 1 year of S-1 (arm B). The primary endpoint was 2-year DFS. The secondary endpoints were feasibility and toxicity. A total of 40 patients were enrolled, but 3 were excluded in accordance with the exclusion criteria. The remaining 37 patients were analyzed. The 2-year DFS rate was 54.2% in arm A and 84.2% in arm B. Overall, 15/18 (83.3%) patients completed 4 cycles of paclitaxel plus carboplatin and 13/19 (68.4%) completed 1-year of S-1adjuvant chemotherapy. Of the 18 (16.7%) patients in arm A, 3 experienced grade 3 or 4 adverse events, while none in arm B experienced such events. Therefore, S-1 chemotherapy for patients with completely resected stage II or IIIA NSCLC was a feasible and safe regimen, and it may therefore be considered as a potential adjuvant chemotherapy option for advanced NSCLC.

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Introduction

The mortality rates of patients with non-small-cell lung cancer (NSCLC) with stage II or IIIA disease remain high. Even when complete surgical resection is performed, the 5-year survival rate is only 54.1% in Japanese patients with pathological (P) stage IIIA disease, 47.4% for P-stage IIB and 32.8% for P-stage IIIA (1). The most frequently observed recurrence is distant metastasis. Adjuvant chemotherapy has been administered to patients with completely resected NSCLC in order to control the cancer cells and to improve patient survival. The efficacy of platinum-based adjuvant chemotherapy has been confirmed in large clinical trials (LACE) (2-4). However, the absolute improvement in the 5-year survival rate was only 5% (5,6). Regimens including cisplatin occasionally cause severe side effects, including renal failure, deafness and gastrointestinal disorders. Furthermore, the ratio of patients who complete the treatment is insufficient, and only a ~11% reduction in mortality has been achieved thus far (7-9). Carboplatin plus paclitaxel chemotherapy has been one of the most frequently used chemotherapy regimens for advanced and recurrent NSCLC (10-12), and is occasionally used as an adjuvant regimen for completely resected NSCLC (13,14). Carboplatin is considered to cause milder side effects compared with cisplatin. Side effects such as neuropathy, neutropenia and thrombocytopenia prevent patients from completing a full 3-week regimen cycle with cisplatin. Bi-weekly paclitaxel plus carboplatin has been identified as a method of reducing such side effects, while maintaining similar efficacy to the 3-week regimen (15). This is mainly due to the fact that carboplatin rarely causes nephrotoxicity, neurotoxicity or ototoxicity, and rarely triggers emesis and thrombocytopenia, unlike cisplatin (16). In the present study, the bi-weekly carboplatin plus paclitaxel regimen was selected for adjuvant chemotherapy. The 2-year DFS with bi-weekly carboplatin plus paclitaxel in patients with stage IB-IIIB completely resected NSCLC was previously reported to be 89.0% (17).

S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is an oral anticancer agent comprising tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate, in a molar ratio of 1:0.4:1 (18), which has achieved the highest response rate among several oral anticancer agents against unresectable advanced carcinomas in phase II studies (19). Postoperative S-1 chemotherapy is one of the standard therapies for gastric cancer in the US, Europe and Japan (20,21). Several clinical trials for NSCLC using S-1 chemotherapy and S-1 + platinum-based chemotherapy have been conducted, with largely favorable findings (22-24). The mean relative dose intensity was 64.6%, and grade 3/4 toxicities occurred at the rate of only 15.4% over a 2-week oral administration of S-1 followed by a 1-week interval (24).

In the present study, the feasibility and tolerability of S-1 as adjuvant therapy for advanced lung cancer was examined.

Patients and methods

Patients. A multicenter randomized feasibility study of paclitaxel plus carboplatin vs. S-1 in patients with locally advanced completely resected NSCLC was conducted. A total of 40 patients underwent complete resection and were diagnosed with pathological stage II or IIIA NSCLC according to the 7th edition of the Tumor-Node-Metastasis classification (25) at the Nagoya City University Hospital (Nagoya, Japan) and its affiliated hospitals, between January 2008 and December 2013. Written informed consent was obtained from all the patients, and the study protocol was approved by the Institutional Review Board of each participating institution. This study was registered on the UMIN Clinical Trial database (ID:000001510).

The eligibility criteria were as follows: Histologically confirmed NSCLC, completely resected, pathological stage II or IIIA disease, no previous chemotherapy or radiotherapy, age 20-75 years, Eastern Cooperative Oncology Group performance status of 0 or 1, white blood cell count 3,500-12,000/mm^3 (normal, 3,000-8,500/mm^3), absolute neutrophil count ≥2,000/mm^3 (normal, 38.3-74.7%), platelet count ≥100,000/mm^3 (normal, 150,000-361,000/mm^3), hemoglobin level ≥10 g/dl (normal, 10.8-14.9 g/dl), aspartate aminotransferase and creatinine level <upper limit of normal (ULN), creatinine clearance rate >60 ml/min, percutaneous oxygen saturation concentration by room air ≥95%, and aspartate aminotransferase, alanine aminotransferase and total bilirubin levels <2 times the ULN; the patients also had to have started chemotherapy within 8 weeks following surgery and been able to receive oral intake. The exclusion criteria were patients with previous chemotherapy or radiotherapy, concomitant malignancy within 5 years, interstitial pneumonia with clinical symptoms, and significant cardiac arrhythmia or heart failure.

Treatment schedule. The randomization was performed centrally at the Department of Oncology, Immunology and Surgery of the Nagoya City University Graduate School of Medical Sciences (Nagoya, Japan). The patients were randomly assigned either to arm A (18 cases) receiving paclitaxel plus carboplatin bi-weekly, or to arm B (19 cases) receiving S-1. The treatments performed in the present study are schematically summarized in Fig. 1. Randomized allocation factors included facility, age, histological type and stage.

The infusing dosage of paclitaxel was 120 mg/m^2 on days 1 and 15. Carboplatin at an area under the curve (AUC) dose of 3 was also administered on days 1 and 15. The patients received adjuvant chemotherapy with paclitaxel plus carboplatin every 4 weeks for up to 4 cycles. The Calvert's formula was used to calculate the dose of the AUC for carboplatin (26), while the creatinine clearance was determined with the Jelliffe formula (27).

The dosage of S-1 was established as follows: Patients with a body surface area (BSA) <1.25 m^2 received 40 mg twice daily (80 mg/day); those with BSA ≥1.25 m^2 but <1.5 m^2 received 50 mg twice daily (100 mg/day); and those with a BSA ≥1.5 m^2 received 60 mg twice daily (120 mg/day). S-1 was administered for 2 weeks followed by a 1-week rest period for up to 1 year. Both arms A and B continued on the above prescription unless there was any evidence of relapse, other malignancies, or severe adverse events.

Throughout the study, the dosage of paclitaxel plus carboplatin was adjusted according to the presence and severity of hematological and non-hematological toxicities. For patients exhibiting evidence of hematological or non-hematological toxicity, the treatment on day 15 was omitted and the dosage for the next course was reduced by one level (from paclitaxel 90 mg m^2 and carboplatin AUC 2, to paclitaxel 60 mg m^2 and carboplatin AUC 2). The dosage of S-1 was also planned to be reduced by 1 level (15 mg/m^2) up to 2 times for patients exhibiting evidence of grade ≥3 hematological or non-hematological toxicities. All dose reductions were limited to two levels.

Recurrence was diagnosed on the basis of imaging study findings. Chest and abdominal computed tomography and positron emission tomography plus head magnetic resonance imaging were performed at 6- and 12-month intervals, respectively. In addition, when the patients complained of any symptoms or exhibited elevated tumor markers on blood tests, imaging studies were performed.

Evaluation of feasibility and toxicity. All the eligible patients who had received any definitive treatment were considered as assessable for feasibility and toxicity. The feasibility was evaluated based on the rate of treatment completion (4 cycles completed for carboplatin plus paclitaxel, and 1 year completed for S-1) and safety (rate of grade ≥3 toxicities). Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (Common Terminology Criteria for Adverse Events) version 3.0 (28).

Statistical analysis. The sample size was determined based on a phase II study reported by Kawamura *et al* applying docetaxel plus gemcitabine as an adjuvant chemotherapy in 35 patients (29). This previous study reported a 2-year DFS rate of ~52%, with a 95% confidence interval (CI) of 35-69%. Based on this result, the expected and threshold values of the 2-year DFS were 40 and 65%, respectively. The number of patients required was determined with an α risk of 0.05 and a β risk of 0.1. The number of patients in each arm was calculated using the Fleming method and found to be 32 per arm. Sufficient data for patients in the present study could not be gathered within the study period. The primary endpoint was the 2-year

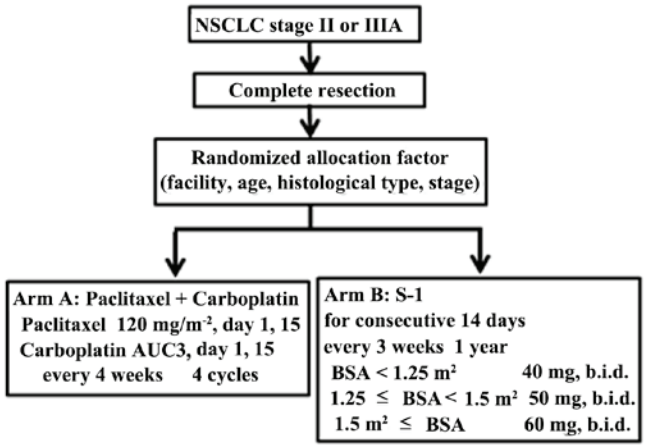

Figure 1. Treatment scheme of the present study. NSCLC, non-small-cell lung cancer; AUC, area under the curve; BSA, body surface area; b.i.d., twice daily.

DFS rate, and the secondary endpoints were the feasibility and toxicity. The characteristics, feasibility, adverse events, DFS and overall survival of 37 patients were analyzed. The cumulative total administration cycles, 2 and 5-year DFS and overall survival (OS) were examined by the Kaplan-Meier method and the difference between the two arms was calculated by the log-rank test. The differences in the rate of adverse events were evaluated by the χ^2 test. All the data were analyzed with EZR software (30). $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

Patient enrollment. A total of 40 patients with stage II or IIIA NSCLC who had received surgically complete resection were enrolled. Of the 40 patients, 3 were excluded in accordance with the exclusion criteria: 1 patient refused to continue participating in this study after registering, 1 patient used another chemotherapy regimen during the follow-up period (under recurrence-free conditions) and 1 patient had a history of multiple cancers. The remaining 37 patients were randomized to either arm (18 cases in arm A and 19 in arm B). The patient characteristics are summarized in Table I. Briefly, the patients included 6 women and 31 men, with a mean age of 62.8 years (range, 39-75 years). In arm A, 2 patients with pneumonectomy (2/37, 5%) were included. These 2 patients completed four cycles of carboplatin plus paclitaxel, but were confirmed to have recurrence within 1 year following surgery. When interpreting the results of the present study, this point should be kept in mind.

Treatment delivery. In total, 50% of the patients in arm A received paclitaxel plus carboplatin and 52.6% of the patients in arm B received S-1, along with the planned schedule and at the planned dose (Table II). In arm B, 1 of the 2 patients refused to continue the treatment due to financial difficulties, and the other interrupted the treatment due to continued grade 1 anorexia.

Feasibility and toxicity. The drug-related adverse events are listed in Table III. The main adverse events in arm A were anaphylaxis, hematological toxicity, neuropathy and alopecia. Two patients developed a grade 4 allergic reaction (anaphylactic shock); however, immediately after cessation of the infusion of paclitaxel, and following treatment with steroid therapy, the patients recovered without sequelae. Both patients discontinued adjuvant chemotherapy with paclitaxel plus carboplatin: 1 patient went on to receive 4 cycles of gemcitabine plus carboplatin as adjuvant therapy, and the other patient received no further adjuvant chemotherapy. There were no grade 3 or 4 adverse events in arm B. Adverse events occurred in 15 patients (83.3%) in arm A, and in 11 patients (57.9%) in arm B; the difference was non-significant (P=0.151). In total, 3 patients (16.7%) in arm A and 6 patients (31.6%) in arm B discontinued drug administration due to adverse events caused by the agent and the patients' wishes. In addition, 6 patients (33.3%) in arm A and 3 (15.8%) in arm B required a dose reduction due to adverse events. No treatment-associated deaths occurred.

Survival. Ultimately, 9 patients (50%) in arm A and 8 (42.1%) in arm B relapsed. In arm A, the relapse sites were the brain (4 cases), the brain and mediastinal lymph nodes (1 case), the bone (1 case), the adrenal glands (1 case), the mediastinum (1 case), and the mediastinum and supraclavicular lymph nodes (1 case). In arm B, the relapse sites were the brain and mediastinal lymph nodes (1 case), the trachea (1 case), the supraclavicular lymph nodes (1 case), the mediastinal lymph nodes (2 cases), and the intrathoracic cavity (3 cases). Two patients were excluded from the analysis of DFS and OS as they were unable to continue paclitaxel plus carboplatin chemotherapy due to an anaphylactic reaction following infusion of paclitaxel. The median follow-up time was 47 months (range, 13-79 months). The 2-year DFS rates were 54.2% (95% CI: 27.1-75.0%) in arm A and 84.2% (95% CI: 58.7-94.6%) in arm B (Fig. 2A). No statistically significant difference in the 2-year DFS was noted between the two arms, although there was a weak tendency toward an improved rate in arm B. For further detailed breakdowns of the effects on survival, the 5-year DFS (Fig. 2A) and OS (Fig. 2B) was also investigated.

Discussion

The survival of patients with advanced lung cancer is unfavorable compared with malignant tumors of other organs (31). However, adjuvant chemotherapy may improve the outcomes of advanced lung cancer patients who have undergone surgically complete resection.

The result of clinical trials in Japan regarding the oral administration of UFT (tegafur and uracil at a 1:4 molar ratio) demonstrated significant survival benefits for stage I patients who have undergone complete surgical resection (32). Platinum-based chemotherapy is used as standard adjuvant chemotherapy for patients with locally advanced (stage II or IIIA) disease (3,4), but its treatment outcomes have been controversial (5,6). Several challenges have been associated with the use of platinum-doublet adjuvant chemotherapy (3,4), such as severe adverse effects, including renal failure, deafness and gastrointestinal toxicity. To reduce the rate and severity of such side effects, several adjuvant chemotherapy regimens have been proposed and evaluated in a series of clinical

Table I. Characteristics of 37 eligible patients.

Characteristics	All patients	PTX + CBDCA	S-1	P-value
Number of patients	37	18	19	
Observation period, months				
Range	13-79	17-75	13-79	0.62
Median	47	39	48	
Sex				
Male	31	14	17	0.405
Female	6	4	2	
Age, years				
Range	39-75	47-73	39-75	0.471
Mean	62.8	62.8	62.9	
Histological type				
Adenocarcinoma	23	10	13	0.379
Squamous cell carcinoma	12	6	6	
Others	2	2	0	
Pathological stage				
IIA	17	9	8	0.98
IIB	11	5	6	
IIIA	9	4	5	
Surgery				
RUL	13	6	7	0.702
RMLL	2	0	2	
RLL	9	4	5	
LUL	6	4	2	
LLL	5	2	3	
Left pneumonectomy	2	2	0	

P-values were calculated using the χ^2 test. RUL, right upper lobectomy; RMLL, right middle and lower lobectomy; RLL, right lower lobectomy; LUL, left upper lobectomy; LLL, left lower lobectomy; PTX, paclitaxel; CBDCA, carboplatin.

trials (7-9). However, no optimal adjuvant chemotherapy has yet been established for advanced lung cancer.

At present, carboplatin doublet chemotherapy has been found to have almost the same effects as cisplatin doublet chemotherapy in the treatment of patients with recurrent and advanced lung cancer (10-12). Paclitaxel plus carboplatin is also considered a standard chemotherapy regimen for recurrent and advanced lung cancer, although several specific side effects, including anaphylactic reaction and neuropathy, may occur (11-13).

In the present study, the efficacy of orally administered S-1 was evaluated as adjuvant chemotherapy for stage II or IIIA patients who had undergone complete surgical resection of their tumors. S-1 is a fluorouracil chemotherapeutic agent used for recurrent and advanced lung cancer as second- or third-line chemotherapy. As S-1 is considered more effective compared with UFT, long-term S-1 administration may be promising as an adjuvant chemotherapy for advanced lung cancer (22). Similar to the results reported by Iwamoto *et al* (22), the present study found adjuvant chemotherapy with long-term S-1 in completely resected stage II-IIIA NSCLC to be safe and effective. In the present study, S-1 therapy was compared with a carboplatin plus paclitaxel regimen, which is associated with fewer and less severe adverse events compared with cisplatin doublet treatment. The efficacy and safety of S-1 adjuvant therapy were similar or better compared with those of carboplatin plus paclitaxel. Indeed, several studies reported that S-1 administration as adjuvant chemotherapy is associated with significant survival benefits following surgically complete

Table II. Administration of treatment.

	Carboplatin + paclitaxel		S-1	
Patients	No.	%	No.	%
Patients following planned schedule and dose	9	50	10	52.6
Patients discontinuing treatment	3	16.7	6	31.6
Patients developing toxicity	3	16.7	4	21.1
Patient refusal	0	0	2	10.5
Patients receiving dose reduction	6	33.3	3	15.8

Table III. Toxicity.

	Carboplatin + paclitaxel (n=19)			S-1 (n=18)		
Adverse events	G1/2 No. (%)	G3 No. (%)	G4 No. (%)	G1/2 No. (%)	G3 No. (%)	G4 No. (%)
Neutropenia	2 (11)	2 (11)		1 (6)		
Leukopenia	4 (21)					
Thrombocytopenia	1 (5)					
Anorexia				2 (11)		
Nausea				1 (6)		
Vomiting	1 (5)					
Elevation of ALT, AST				3 (17)		
Elevation of bilirubin				1 (6)		
Neuropathy (sensory)	6 (32)					
Fatigue	1 (5)					
Alopecia	4 (21)					
Urticaria				2 (11)		
Anaphylaxis			2 (11)			
Stomatitis				1 (6)		
Weight loss				1 (6)		
Others	3 (16)			5 (28)		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade.

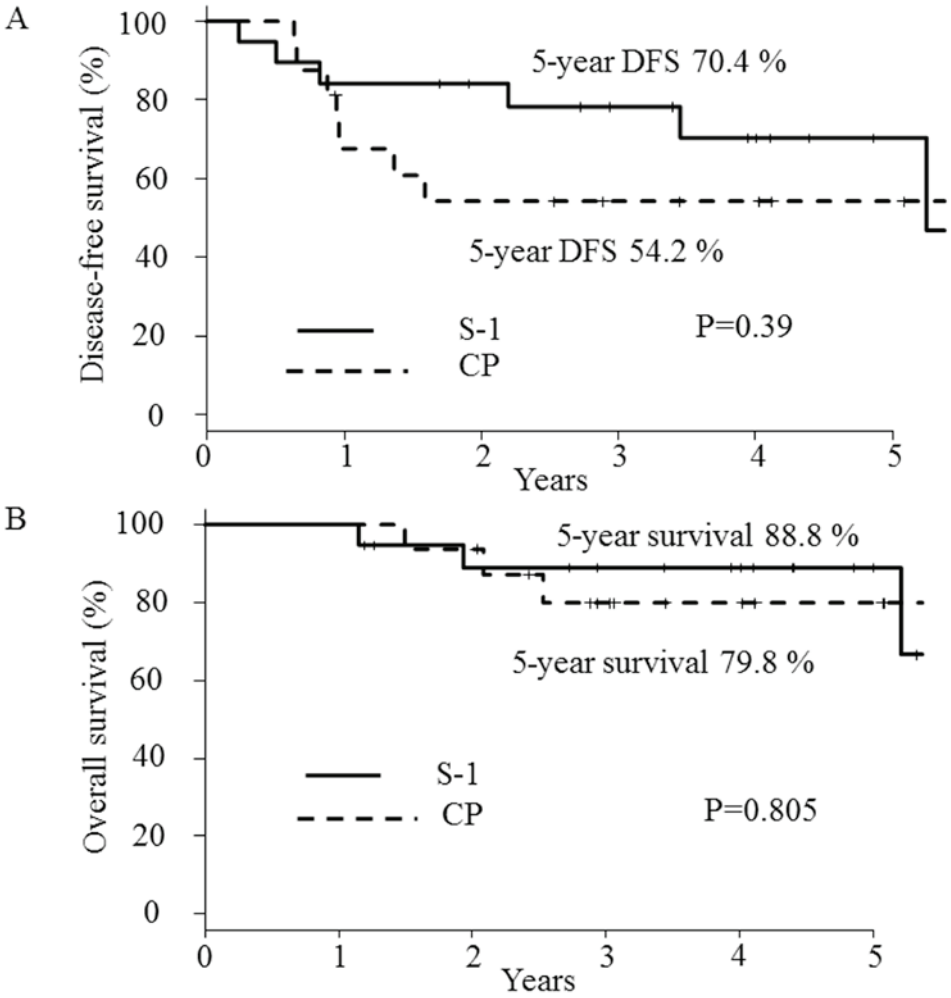

Figure 2. Kaplan-Meier estimates of (A) disease-free and (B) overall survival. DFS, disease-free survival; CP, carboplatin + paclitaxel.

resection for gastric cancer, squamous cell carcinoma of head and neck, breast cancer and NSCLC (19,22-24,33,34). The 5-year DFS and OS were almost the same between the S-1 group and the paclitaxel plus carboplatin group. As the side effects of S-1 were tolerable, S-1 chemotherapy may be considered to be a promising adjuvant chemotherapy for patients with advanced disease who have undergone complete surgical resection.

Several studies have investigated the optimal regimen for S-1 administration. One previous study reported that a treatment schedule of a 2-week administration followed by a 1-week interval appears more feasible and safer compared with the conventional 4-week administration followed by a 2-week interval (35). Considering this report, a treatment schedule of 2-week administration followed by a 1-week interval was selected for the present study; although the adverse events associated with S-1 treatment were of grade 1 or 2, and the majority were controllable, 6 patients discontinued treatment, resulting in an unsatisfactory completion rate of S-1 adjuvant therapy. Therefore, a more feasible administration schedule for S-1 as adjuvant therapy for advanced lung cancer must be developed. The main limitation of the present study was the small patient population. Further large-scale clinical trials with a longer administration period for S-1 are required. Overall, the results of the present study demonstrated that S-1 treatment for 1 year with a 2-week administration followed by a 1-week interval appeared to be tolerable and safe as an adjuvant chemotherapy regimen.

In conclusion, the 2-year DFS rate as the primary endpoint was found to be acceptable. S-1 chemotherapy for patients with completely resected stage II or IIIA NSCLC was feasible and safe, and it may therefore be considered as an option for adjuvant chemotherapy in advanced NSCLC.

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