A multi-institutional phase II study of combination chemotherapy with S-1 plus cisplatin in patients with advanced non-small cell lung cancer

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Received September 22, 2010; Accepted December 23, 2010

DOI: 10.3892/ol.2011.266

Abstract. S-1 is an oral anticancer fluoropyrimidine agent designed to elevate anticancer activity with a decrease in gastrointestinal toxicity. We conducted a phase II study to evaluate the efficacy and safety of combination chemotherapy with S-1 plus cisplatin in patients with advanced non-small cell lung cancer (NSCLC). Chemotherapy-naïve patients were treated with S-1 administered orally at 40 mg/m^2 twice a day for 21 consecutive days, and cisplatin (60 mg/m^2) infused intravenously on day 8, repeated every 5 weeks. Of the 44 patients enrolled in the study, 40 were assessable for efficacy and safety. The median number of cycles administered was 3 (range 1-9 cycles). Among the 40 assessable patients, 7 partial responses were observed, with an overall response rate (RR) of 17.5% [95% confidence interval (CI), 5.2-29.8]. Patients with squamous cell carcinoma showed a significantly higher RR (55.5%) than those with adenocarcinoma (9.1%) or other types of NSCLC (0%). The median progression-free survival was 4.3 months (95% CI, 3.4-4.9), the median survival time was 17.9 months (95% CI, 15.0-20.8), and the 1- and 2-year survival rates were 63.3 and 27.3%, respectively. Major grade 3-4 hematologic toxicities were leukocytopenia (7.5%), neutropenia (5.0%), anemia (15.0%) and thrombocytopenia (2.5%). No grade 4 non-hematologic toxicity or treatment-related death occurred. These results suggest that combination chemotherapy with S-1 plus cisplatin is a promising therapeutic candidate for patients with advanced NSCLC, particularly squamous cell carcinoma.

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Abbreviations: NSCLC, non-small cell lung cancer; 5-FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine; RR, response rate; MST, median survival time; CDDP, cisplatin; ECOG, Eastern Cooperative Oncology Group; BSA, body surface area; PFS, progression-free survival; 95% CI, 95% confidence interval; PR, partial response; SD, stable disease; PD, progressive disease; TP, thymidine phosphorylase; DPD, dihydropyrimidine dehydrogenase

Key words: combination chemotherapy, S-1, cisplatin, non-small cell lung cancer

Introduction

Lung cancer is the leading cause of malignancy-related death worldwide, with a mortality rate of 80-90% (1). Among patients with lung cancer, 85% are diagnosed as having non-small cell lung cancer (NSCLC). Despite efforts, innovations, and progress in the diagnosis and treatment of these patients, patient survival at 5 years after diagnosis is only 15% (1). Therefore, novel therapeutic strategies to improve the outcome of patients with NSCLC are urgently required.

S-1 is an oral anticancer fluoropyrimidine agent comprising the 5-fluorouracil (5-FU) prodrug tegafur and two enzyme inhibitors, 5-chloro-2, 4-dihydroxypyridine (CDHP) and potassium oxonate (2,3). Since CDHP inhibits dihydropyrimidine dehydrogenase activity and potassium oxonate suppresses pyrimidine phosphoribosyl transferase activity, oral S-1 administration generates a higher concentration of 5-FU than a protracted intravenous injection of 5-FU, without increasing the incidence

of adverse events in the gastrointestinal tract (4-6). In a phase II trial, involving monotherapy with S-1 at 80 mg/m^2/day for 28 days followed by a 2-week rest period in chemotherapy-naïve patients with advanced NSCLC, the overall response rate (RR) was 22.0% and the median survival time (MST) was 10.2 months (7). Moreover, two phase II trials of S-1 plus cisplatin (CDDP) for advanced NSCLC (stage IIIB, without any indication for radiotherapy, or stage IV) yielded RRs of 32.7-47% and MSTs of 11-16 months with a mild toxicity profile (8,9). Recent evidence has indicated favorable efficacy of S-1 in combination with chemotherapeutic agents, with the exception of CDDP, for advanced NSCLC (10,11). Although the results suggest the efficacy of combinations of S-1 with other chemotherapeutic agents, the therapeutic efficacy and safety of combination chemotherapy with S-1 plus CDDP in patients with advanced NSCLC have yet to be elucidated.

In the present study, a phase II study of combination chemotherapy with S-1 (40 mg/m^2 twice a day on days 1-21 followed by a 2-week rest) and CDDP (60 mg/m^2 on day 8, every 5 weeks) was conducted in patients with advanced NSCLC, and the efficacy and safety of this regimen were determined. The MST of 17.9 months occurred over a longer period of time, and the incidence of adverse events was lower than that for standard NSCLC chemotherapy. Furthermore, an overall RR in patients with squamous cell carcinoma was statistically superior compared with that in patients with adenocarcinoma or other types of NSCLC. These findings suggest that combination chemotherapy with S-1 plus CDDP is a promising therapeutic candidate for patients with advanced NSCLC, particularly squamous cell carcinoma.

Patients and methods

Patient eligibility. Patients were eligible for this phase II trial in the event that they were either cytologically or histologically confirmed to have NSCLC; were in stage IIIB, without any indication of radical thoracic radiotherapy, or stage IV; had measurable disease; received no prior treatment; were in the age range of 20-74 years; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and had a projected life expectancy of at least 3 months. Other eligibility criteria for organ function included: leukocyte count 4000-12,000/μl, absolute granulocyte count ≥2000/μl, platelet count ≥100,000/μl, hemoglobin level ≥9 g/dl, serum bilirubin level ≤1.5 mg/dl, serum aspartate aminotransferase and alanine amino transferase levels ≤100 IU/l, alkaline phosphatase level of twice the upper limit or less, normal creatinine level, creatinine clearance rate of ≥60 ml/min, and arterial oxygen partial pressure of ≥60 Torr. Since S-1 is in tablet form, patients were required to be able to swallow. For staging, all 44 patients underwent a computed tomography scan of the thorax, including upper abdomen, and either a brain computed tomography scan or magnetic resonance imaging of the brain. A radioisotopic bone scan was also performed in the majority of the patients.

Exclusion criteria included pregnancy or serious concomitant disease, concomitant malignancy, pleural effusion requiring treatment, or symptomatic cerebral involvement. Written informed consent was obtained from all patients, and the protocol was approved by the Institutional Review Board of each of the participating institutions. On enrollment to the study, the eligibility of the patients was reviewed by the Central Administration Office at the Department of Respiratory Medicine and Rheumatology, University of Tokushima, Japan.

Treatment schedule. Oral administration of S-1 at 40 mg/m^2 occurred twice a day, after meals, on days 1-21. The actual dose of S-1 administration was selected as follows: in a patient with a body surface area (BSA) <1.25 m^2, 40 mg twice a day; BSA of 1.25 m^2 but <1.5 m^2, 50 mg twice a day; and BSA ≥1.5 m^2, 60 mg twice a day. CDDP (60 mg/m^2) was administered intravenously on day 8 when patients were hydrated by infusion of at least 2,500 ml. Administration of an antiemetic agent was permitted at the discretion of each patient's physician. The treatment regimen was repeated every 5 weeks until disease progression or unacceptable toxicity occurred. A leukocyte count of ≥3000/μl, an absolute granulocyte count of ≥1500/μl, a platelet count of ≥100,000/μl and the entry eligibility criteria regarding organ functions had to be achieved in order for the following cycle to commence. If these criteria were satisfied 4 weeks after day 1 of each cycle of chemotherapy, administration of the following cycle was allowed. The doses of S-1 were adjusted according to the degree of hematologic and non-hematologic toxicity. The dose was reduced by one level (20 mg per day) in patients with evidence of grade 4 hematologic toxicity or grade ≥3 non-hematologic toxicity during any cycle of administration. If recovery from such toxicities was confirmed at a reduced dose, administration at the reduced dose was continued. If a rest period of ≥3 weeks was required, the patient was withdrawn from the study.

Evaluation of response and toxicity. Eligible patients who received at least one course of S-1 plus CDDP were considered assessable for response and toxicity. Chest X-ray, complete blood count, and blood chemistry studies were repeated at least once a week. The response was assessed based on the computed tomography scan findings that had been used initially to define the extent of the tumor. The response was evaluated at the end of each treatment cycle in accordance with the Response Evaluation Criteria in Solid Tumors version 1.0. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0.

Statistical analysis. The primary end point was RR; secondary end points included progression-free survival (PFS), overall survival and adverse events. PFS was defined as the time from registration to progression or death from any cause. Overall survival was defined as the time from registration to death from any cause or when the patient was last known to be alive. The minimum number of patients to be enrolled in this study was defined as 34, with the assumption that the 95% CI would be 30% under conditions giving an α error of 0.025 (one-sided) and a β error of 0.2, assuming an anticipated RR of 50%. Consequently, 40 patients were included to allow for patient dropout. The median PFS and MST were estimated by the Kaplan-Meier method of univariate analysis. The differences between categorized groups were compared by the one-way ANOVA test. All statistical tests were two-sided, and $p<0.05$ was considered to be statistically significant.

Table I. Patient characteristics.

No. of patients	40	
Age (years)		
Median (range)	64	(27-74)
Gender		
Male	32	(80.0%)
Female	8	(20.0%)
Performance status (ECOG)		
0	12	(30.0%)
1	28	(70.0%)
Stage		
IIIB	13	(32.5%)
IV	27	(67.5%)
Histology		
Adenocarcinoma	22	(55.0%)
Squamous cell carcinoma	9	(22.5%)
Others	9	(22.5%)

ECOG, Eastern Cooperative Oncology Group.

Results

Patient population. Between July 2005 and November 2008, 44 patients with advanced NSCLC from 7 institutions were enrolled in this study. Of the 44 patients, 40 were assessable for efficacy and safety. Two patients were excluded since they declined entry to the study after enrollment. Two other patients were considered not to be assessable as they were unable to receive any CDDP due to high fever and massive pleural effusion, respectively, after S-1 treatment had commenced. The clinical characteristics of the 40 assessable patients are shown in Table I. Patients included 32 males (80%) and 8 females (20%). The median age was 64 years (range 27-74). The patients had an ECOG performance status of 0 (12/40, 30%) or 1 (28/40, 70%). A total of 13 patients (32.5%) had stage IIIB and 27 (67.5%) had stage IV NSCLC. The predominant histological type was adenocarcinoma (55%), followed by squamous cell carcinoma (22.5%) and other types of NSCLC (22.5%).

Response and survival. No complete response (CR) was observed in the 40 patients, whereas 7 patients showed a partial response (PR), yielding an overall RR of 17.5% (95% CI 5.2-29.8). Stable disease (SD) was observed in 25 patients (62.5%). Thus, the disease control rate (PR+SD) was 80% (95% CI 67.1-92.9). Eight patients (20%) showed progressive disease (PD). Table II shows patient characteristics in relation to response. No statistically significant differences were noted in the RRs among gender and stages. Notably, the overall RR in patients with squamous cell carcinoma (55.5%) was statistically superior compared with the RR in patients with adenocarcinoma or other types of NSCLC (9.1%, p=0.012; 0.0%, p=0.009, respectively). The MST of the 40 assessable patients was 17.9 months (95% CI 15.0-20.8), and the 1- and 2-year survival rates were 63.3 and 27.3%, respectively (Fig. 1). As shown in Fig. 2, the median PFS was 4.3 months (95% CI 3.4-4.9). Exploratory analyses of the survival according to histological subtypes showed no significant differences in the MST and median PFS. The MSTs and median PFSs of patients with squamous cell carcinoma, adenocarcinoma and other types of NSCLC were 21.1 and 6.5 months, 17.9 and 4 months, and 14.5 and 4.2 months, respectively.

Adverse events. Table III shows the major adverse events in the 40 assessable patients during the entire treatment period. The hematological adverse events reaching grades 3-4 were anemia (15%), leukocytopenia (7.5%), neutropenia (5%) and thrombocytopenia (2.5%). Febrile neutropenia was observed in only one patient (2.5%). Grade 3 non-hematologic adverse events were anorexia (12.5%), nausea/vomiting (7.5%), infection (5%), general fatigue (2.5%) and gastric ulcer (2.5%). No cases

Table II. Patient characteristics in relation to the response.

		Response				
Characteristics	No. of patients	CR	PR	SD	PD	Response rate (%)
No. of patients	40	0	7	25	8	17.5
Gender						
Male	32	0	5	19	8	15.6
Female	8	0	2	6	0	25.0
Stage						
IIIB	13	0	2	8	3	15.4
IV	27	0	5	17	5	18.5
Histology						
Adenocarcinoma	22	0	2	15	5	9.1
Squamous cell carcinoma	9	0	5	3	1	55.5
Others	9	0	0	7	2	0.0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

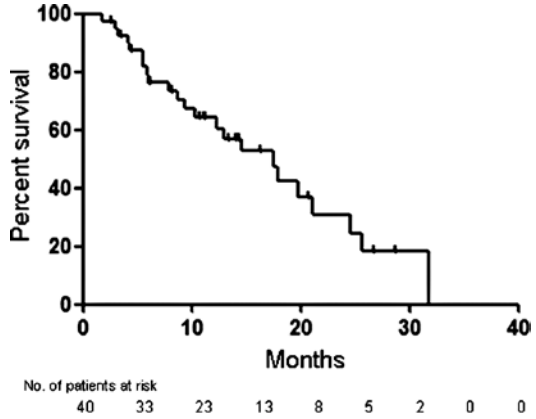

Figure 1. Overall survival of 40 assessable patients was calculated according to the Kaplan-Meier method. The median survival time was 17.9 months (95% CI 15.0-20.8), and the 1- and 2-year survival rates were 63.3 and 27.3%, respectively.

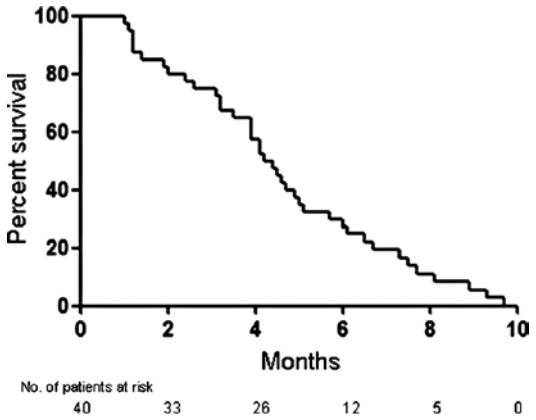

Figure 2. Progression-free survival of 40 assessable patients was calculated according to the Kaplan-Meier method. The median progression-free survival was 4.3 months (95% CI 3.4-4.9).

of grade 4 toxicity occurred. Moreover, no instance of irreversible toxicity or treatment-related death was noted.

Compliance. The median number of cycles administered was 3, with a range of 1-9 treatment cycles (1 cycle, 7 patients; 2 cycles, 9 patients; 3 cycles, 8 patients; 4 cycles, 12 patients; ≥5 cycles, 4 patients). The reasons for administration of only one cycle of treatment were PD in 5 patients and adverse events in 2 patients. A total of 122 cycles were administered to the 40 patients. Seven patients required temporary or permanent cessation in S-1 during the treatment courses due to adverse events, including myelosuppression in 4 patients, pulmonary toxicity in 2, and gastrointestinal toxicity in 1 patient. No dose reduction of S-1 was required in any of the 40 assessable patients. CDDP administration was disregarded in 4 patients due to myelosuppression, and the dose of CDDP was reduced in 1 patient due to gastrointestinal toxicity.

Discussion

The present study indicates that combination chemotherapy with S-1 plus CDDP may constitute an efficacious and well-tolerated therapeutic option for patients with treatment-naïve advanced NSCLC. The MST of 17.9 months occurred over a longer period of time, and the incidence of adverse events was lower than the values for the standard NSCLC chemotherapy. Consequently, combination chemotherapy with S-1 plus CDDP is a promising therapeutic candidate for patients with advanced NSCLC.

Table III. Hematologic and non-hematologic toxicities.

Adverse events	Grade			Grade 3-4
	2	3	4	(%)
Leukocytopenia	7	3	0	7.5
Neutropenia	6	2	0	5.0
Anemia	8	4	2	15.0
Thrombocytopenia	5	0	1	2.5
Liver disorder	4	0	0	0.0
Bilirubin	1	0	0	0.0
Creatinine	2	0	0	0.0
Hyponatremia	0	1	0	2.5
Infection	0	2	0	5.0
Anorexia	6	5	0	12.5
Nausea/vomiting	7	3	0	7.5
General fatigue	4	1	0	2.5
Gastric ulcer	0	1	0	2.5
Diarrhea	2	0	0	0.0
Constipation	1	0	0	0.0
Stomatitis	1	0	0	0.0
Desquamation	1	0	0	0.0
Fever	1	0	0	0.0

A phase II trial of combination chemotherapy with S-1 at 80 mg/m^2/day for 21 days and CDDP at 60 mg/m^2 on day 8 yielded a RR of 47.3% and a MST of 11 months (8). Ozawa *et al* also reported a phase II study of combination chemotherapy with S-1 at 80 mg/m^2/day for 21 days and weekly CDDP at 25 mg/m^2/week on days 7, 14 and 21, which yielded a RR of 23.1% and a MST of 13.4 months (9). Compared with the reported RRs and MSTs of 17-28% and 7-9 months, respectively, for standard platinum-doublet chemotherapy regimens in patients with advanced NSCLC (12,13), the combination of S-1 with CDDP appears to be encouraging. In the present study, combination chemotherapy with S-1 (80 mg/m^2/day, days 1-21) and CDDP (60 mg/m^2 on day 8, every 5 weeks) yielded a potentially longer MST (17.9 months) than that for the abovementioned studies, despite the relatively low RR (17.5%). The modest improvement in survival observed in this study as compared with previous studies may be affected by various factors including the high rate of SD (62.5%), which extended the disease control rate to 80.0%, or the exclusion of patients with a performance status of 2. In addition, second- and/or third-line chemotherapy treatments may prolong the survival of patients with advanced NSCLC, as previously reported (14,15). In this study, 37 patients (92.5%) received second-line chemotherapy, involving platinum-based doublet chemotherapy, non-platinum-doublet chemotherapy, single

non-platinum antitumor agent and epidermal growth factor receptor tyrosine kinase inhibitors in 16 (43.2%), 7 (18.9%), 9 (24.3%) and 5 (13.5%) patients, respectively. Among these 37 patients, 35 were assessable for response. PR and SD were observed in 4 (11.4%) and 21 (60.0%) patients, respectively, yielding a disease control rate (PR+SD) of 71.4%. Although a much longer MST (17.5 months) was observed in the present study, the median PFS (4.3 months) was comparable to or tended to be shorter than that in previous studies (10,11), indicating that additional chemotherapy treatments following the failure of first-line combination treatment with S-1 and CDDP may have a favorable survival effect.

Accumulating evidence has shown that the histological types of NSCLC affect the clinical outcome of patients treated with anticancer drugs (16,17). A phase III study showed a significant survival difference in favor of CDDP/pemetrexed compared with CDDP/gemcitabine in patients with adenocarcinoma and large-cell carcinoma but not in those with squamous cell carcinoma (16). Consequently, pemetrexed is approved for use in combination with CDDP for first-line treatment in patients with advanced non-squamous NSCLC. Moreover, serious hemorrhagic events have been reported to occur more frequently among patients with squamous cell carcinoma treated by bevacizumab (17). Therefore, patients with advanced squamous cell carcinoma have been routinely excluded from bevacizumab treatment, while the addition of bevacizumab to carboplatin/paclitaxel in the treatment of patients with non-squamous NSCLC has a significant survival benefit. These findings indicate the disadvantages of NSCLC patients with squamous histology, since they cannot benefit from these drugs and have fewer treatment options than those with non-squamous histology. Notably, in the present study, a significantly higher RR was observed in patients with squamous cell carcinoma (55.5%) than in those with adenocarcinoma (9.1%) or other types of NSCLC (0.0%). Given the small sample size, these data should be interpreted with caution. It is noteworthy, however, that combination chemotherapy with S-1 plus CDDP may confer treatment benefit on lung cancer patients with squamous cell histology. One potential explanation for this outcome may relate to thymidine phosphorylase (TP) and dihydropyrimidine dehydrogenase (DPD) expression levels in NSCLC histological types. The ratio of TP to DPD is considered to be a useful predictor of the efficacy of chemotherapy with 5-FU, since TP converts 5'-deoxy-5-fluorouridine to 5-FU and DPD inactivates 5-FU in tumor tissue (18). Moreover, the ratio of TP to DPD in NSCLC tissue was reported to be higher in squamous cell carcinoma than in adenocarcinoma (19). These findings indicate that chemotherapy with 5-FU is potentially more effective in lung cancer patients with squamous cell carcinoma than in those with adenocarcinoma. To the best of our knowledge, this is the first study to show the significant treatment benefit of this combination in lung cancer patients with squamous cell histology as compared to non-squamous NSCLC. Further prospective randomized controlled clinical trials are required to confirm these results.

In platinum-doublet chemotherapies, which are the standard first-line regimen for advanced NSCLC, grade 3/4 neutropenia and gastrointestinal toxicity have been reported in 57-76 and 4-35% of patients, respectively (12,13). By contrast, combination chemotherapy with S-1 plus CDDP is reportedly less toxic than standard platinum-doublet regimens. Findings of phase II studies of combination chemotherapy with S-1 and CDDP have shown grade 3/4 hematologic and non-hematologic toxicities in 22-35 and 4-13% of patients, respectively (8,9). In the present study, mild toxicity profiles were noted for combination chemotherapy with S-1 plus CDDP, consistent with previous reports (8,9). With regards to hematologic adverse events, grade 3/4 leukocytopenia, neutropenia, anemia and thrombocytopenia were observed in 3 (7.5%), 2 (5%), 6 (15%) and 1 (2.5%) patients, respectively. Only 1 patient (2.5%) developed febrile neutropenia. Regarding non-hematologic adverse events, grade 3 infection, anorexia, nausea/vomiting, general fatigue and gastric ulcer were observed in 2 (5%), 5 (12.5%), 3 (7.5%), 1 (2.5%) and 1 (2.5%) patients, respectively. No grade 4 level toxicity occurred, and no instance of irreversible toxicity or treatment-related death was noted. The results indicate the efficacy and safety of combination chemotherapy with S-1 and CDDP for advanced NSCLC.

In conclusion, we investigated the efficacy and safety of a combination regimen of S-1 with CDDP for the treatment of chemotherapy-naïve patients with advanced NSCLC. Results showed a potentially long MST with comparatively low toxicity, indicating that this regimen is a potentially useful alternative therapeutic strategy for patients with advanced NSCLC, particularly squamous cell carcinoma.

Acknowledgements

This study was supported in part by a Grant-in-aid for Cancer Research from the Ministry of Education, Science, Sports and Culture of Japan, and the Ministry of Health and Welfare of Japan.

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