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Phase I/II study of S-1 plus carboplatin in patients with advanced non-small cell lung cancer

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ABSTRACT

The objective of this phase I/II study was to determine the recommended dose (RD) of S-1 and carboplatin (CBDCA), and to evaluate the efficacy and safety of this combination in the treatment of patients with advanced non-small cell lung cancer (NSCLC). Chemotherapy-naïve patients were treated with S-1 given orally on days 1–14, and CBDCA infused intravenously on day 1, repeated every 3 weeks. RD was AUC5 of CBDCA and 80 mg/m^2 of S-1. Nineteen patients were treated at the RD. The overall response was 30.8% (95% confidence interval: 17.1–58.3%). The response rate in the RD was 36.8% (95% CI: 16.3–61.6%). The median overall survival time was 11.1 months (95% CI: 8.1–15.3 months) and the median progression-free survival time was 5.0 months (95% CI: 3.6–6.0 months). Major grades 3–4 toxicities were thrombocytopaenia (47%), anaemia (26%) and infection (16%). This is the first report to show promising activity of this combination in phase II, including survival data and manageable toxicity, especially in outpatients receiving treatment for advanced NSCLC.

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1. Introduction

Lung cancer is a leading cause of cancer mortality in many countries.[1] Combination chemotherapy with platinum agents and new-generation non-platinum anti-tumour agents, for example, paclitaxel, docetaxel[2], vinorelbine[3] and gemcitabine[4], has been regarded as the standard treatment for advanced stage non-small cell lung cancer (NSCLC)[5], although outcomes are far from acceptable.

S-1, a fourth-generation oral fluoropyrimidine, is a formulation of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1.[6] FT is the prodrug for cytotoxic fluorouracil (FU) and CDHP prevents its degradation. CDHP is a potent and competitive

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inhibitor of dihydropyrimidine dehydrogenase, which reduces the degradation of FU and allows efficacious concentrations to enter the anabolic pathway.[7] Oral S-1 administration can generate a higher concentration of 5-FU than protracted intravenous injection of 5-FU, without increasing the incidence of adverse events affecting the gastrointestinal tract.[8]

In a phase II study, which involved monotherapy with S-1 at 80 mg/m^2/day for 28 d followed by a 2-week rest period in chemotherapy-naïve advanced NSCLC patients, the overall response rate was 22%, and the median survival time (MST) was 10.2 months.[9] Combination chemotherapy with cisplatin (60 mg/m^2 on day 8) and S-1 (80 mg/m^2, from days 1 to 21) every 5 weeks resulted in a response rate of 47% and a MST of 11.0 months.[10] Although cisplatin is a basic drug for advanced NSCLC, the relative dose intensity of cisplatin with this regimen was 12 mg/week, considerably lower than the standard (23–27 mg/week). Furthermore, intravenous injection of cisplatin requires hospitalisation for hydration, i.e. to prevent renal toxicity, which negates the advantage and convenience of S-1 as an orally administrated drug allowing outpatient treatment. Carboplatin-based regimens that are less toxic, convenient and capable of being administered on an outpatient basis, thereby maintaining the patient's quality of life, need to be developed. However, there were no confirmed data about fix doses of combination of S-1 plus carboplatin in advanced stage NSCLC as first-line setting.

We conducted the present phase I/II study with oral administration of S-1 for 14 consecutive days and carboplatin on day 1 every 3 weeks in chemotherapy-naïve patients with advanced NSCLC, and determined the efficacy and safety of this regimen.

2. Patients and methods

2.1. Objective

The objective of this study was to determine the maximum tolerable dose (MTD), the toxicity profile, the RD and the setting of dose-limiting toxicity (DLT), and to evaluate efficacy and safety, in chemotherapy-naïve patients with advanced NSCLC.

2.2. Eligibility criteria

Chemotherapy-naïve patients with histologically or cytologically confirmed stage IIIB NSCLC, diagnosed as having no treatment indications for thoracic irradiation, or stage IV, were eligible. Cases with recurrent disease after curative surgery were also eligible. Adjuvant chemotherapy was not counted as one regimen. At least one measurable lesion was necessary as part of the phase II trial. Other eligibility criteria included being 20 to 75 years of age, Eastern Cooperative Oncology Group performance status (PS) of 0–1, adequate organ function (white blood cell count (WBC) $\geqslant$ 4000/μL, platelet count $\geqslant$ 100,000/μL, haemoglobin concentration $\geqslant$ 9.0 g/dL, serum bilirubin $\leqslant$ 2.0 mg/dL, AST and ALT $\leqslant$ 100 IU/L, serum creatinine $\leqslant$ institutional upper limit of normal range; $PaO_2 \geqslant 60$ mmHg). The main exclusion criteria were: active concomitant malignancy, congestive heart failure, uncontrolled angina pectoris, arrhythmia, hypertension, uncontrolled diabetes, symptomatic infectious disease, severe haemorrhage/bleeding, pulmonary fibrosis or interstitial pneumonia, obstructive bowel disease or severe diarrhoea, symptomatic peripheral effusion, cardiac effusion and ascites, symptomatic brain metastasis and pregnancy or breast feeding. This study was approved by the institutional review board at each participating centre. All patients gave written informed consent prior to registration.

2.3. Treatment plan

Patients received variable doses of intravenous carboplatin administered as a 60-min infusion on day 1 and variable doses of oral S-1 administered on days 1–14, every 3 weeks. Carboplatin doses were determined using serum creatinine values and the Calvert formula[11] based on the targeted area under the time-concentration curve (AUC). Patients were treated for at least four cycles unless disease progression or unacceptable toxicity was observed. S-1 administration was interrupted when grade 4 neutropaenia, grade 4 thrombocytopaenia or grade 3 or more severe non-haematological toxicity developed, and was reinitiated when neutrophil counts $\geqq$ 1000//μL, platelet counts $\geqq$ 75000//μL and non-haematological toxicity of grade 2 or less were observed. Subsequent chemotherapy was initiated when the leukocyte counts $\geqq$ 4000//μL, platelet counts $\geqslant$ 100,000/μL, haemoglobin concentration $\geqslant$ 9.0 g/dL, serum creatinine $\leqslant$ 1.5 g/dL, $PaO_2 \geqslant 60$ mmHg and non-haematological toxicity of grade 2 or less were observed.

2.4. Dose escalation

The dose escalation schedule is shown in Table 2. At least three patients were enrolled at each dose level. Initially, three treated patients were treated at dose level 1 and no intra-individual dose escalation was performed. If one DLT was observed in the first three patients, three more patients were enrolled at this dose level, and dose escalation continued to the next level if fewer that three of the six patients experienced DLT during the first cycle. The MTD was defined as the level prior to that at which DLT was observed in two of three or in three of six patients during the first cycle. If all three patients experienced a DLT at level 1, a dose reduction to level 0 was planned. DLTs were defined as: (a) grade 4 neutropaenia lasting 5 d or longer; (b) febrile neutropaenia (grade 3 or 4 neutropaenia with fever (>38.5 °C)); (c) grade 4 thrombocytopaenia; (d) grade 3 or 4 non-haematological toxicity except for nausea, vomiting, anorexia, general fatigue and alopecia; (e) any unresolved toxicity, requiring a delay in administration of the second course exceeding 14 d and (f) inability to administer S-1 for more than seven consecutive days during treatment. Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not allowed at any time during this study.

2.5. Patient evaluation

Haematological and biochemical tests, PS and clinical symptoms were monitored at least once a week. Toxicities were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0 (NCI CTCAE V 3.0;

Table 1 – Patient characteristics.

Number of patients	28
Age, years; median (range) 6 (37–73)	66 (37–73)
Gender	
Male	20
Female	8
Performance status (ECOG)	
0	7
1	21
UICC-Stage	
IIIB	4
IV	24
Histology	
Adenocarcinoma	20
Squamous cell carcinoma	4
Large cell carcinoma	3
Others	1
Prior treatment	
Surgery	
Excision of cranial metastasis	2
Radiation therapy	
Whole brain radiotherapy	3
Palliative radiotherapy	1

available from http://ctep.info.nih.gov/CTC3/ctc.html). Tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST).[12] Time to progression and overall survival were estimated using the Kaplan–Meier method.

2.6. Statistical analyses

A one-stage design using the binominal probability was used to determine the sample size. Assuming that a response rate of 30% would indicate potential usefulness, whereas a rate of 10% would be the lower limit of interest, and with $\alpha = .05$ (one-side) and $\beta = .20$, the estimated accrual number was 24 patients.

3. Results

3.1. Patient characteristics

Between June 2005 and February 2007, 28 patients were enrolled in this study and their characteristics are listed in Table 1. Median age was 62 years (range 37–73). Twenty patients were male and six were female. All patients had good PS (ECOG 0 or 1). Four patients had stage IIIB, and were considered to have no indications for thoracic irradiation, and 24 patients had stage IV. The predominant histological type was adenocarcinoma (71%). Two patients had undergone surgical removal of brain metastases and four patients had received radiation therapy for brain metastasis or pain control.

3.2. Toxicities and dose escalation

Three patients each were entered at levels 1 and 2, and no DLTs were observed (Table 2). The next cohort of three patients received dose level 3 and one patient experienced a delay of more than 2 weeks (38 d) from the starting date of the second course due to thrombocytopaenia. Therefore, one of the first three patients had experienced DLT, when this group was expanded to six patients. Two of three additional patients also experienced delays of more than 2 weeks in starting the second course. One patient could not start the second course after a delay of more than 40 d due to thrombocytopaenia. Another patient started the second course after a delay of more than 18 d due to leucopaenia; thus, three of six patients had DLTs at level 3. Therefore, level 2 was regarded as the RD for the phase II study.

An additional 16 patients were added to level 2, such that 19 patients in total received AUC5 carboplatin on day 1 and 80 mg/m^2 S-1 on days 1–14, every 3 weeks. The median number of treatment cycles was 4 (range 2–6). The major adverse events during the entire treatment period are shown in Table 3. The haematological adverse events reaching grades 3–4 were anaemia (26%), thrombocytopaenia (47%) and leukocytopaenia (10.5%). Of these events, grade 4 thrombocytopaenia and anaemia were observed in one patient, and grade 4 thrombocytopaenia in another. Grades 3–4 non-haematological toxicities were gastritis, anorexia, nausea/vomiting, fatigue and elevation of total bilirubin in one patient each. Grade 3 infection (16%) was observed in three patients (two pneumonias; one pleuritis). There were no irreversible toxicities or treatment-related deaths in this study.

3.3. Efficacy

In level 3, three patients could not start the second course due to haematological toxicities, and in two of the three patients, the response could not be evaluated because of short observation until the start of 2nd line chemotherapy. Among the 26 evaluable patients, eight had a partial response (Table 4). Thus, the overall response was 30.8% (95% confidence

Table 2 – DLTs.

Level	1	2	3
CBDCA (AUC)	5	5	6
S-1 (mg/m^2)	65	80	80
Number of patients	3	3	6
Number of patients with any DLT/Number of patients	0/3	0/3	3/6[a]

a Dose-limiting toxicities, by definition, required a delay in administration of the second course exceeding 14 d. CBDCA, carboplatin; AUC, area under the curve.

Table 3 – Haematological and non-haematological adverse events (n = 28).

Adverse events	1	2	3	4
Haematological toxicity				
Leukocytopaenia	3	4	2	0
Neutrocytopaenia	5	9	0	0
Anaemia	3	5	4	1
Thrombocytopaenia	2	6	7	2
Non-haematological toxicity				
Gastritis	1	0	1	0
Stomatitis	2	1	0	0
Diarrhoea	0	0	0	0
Constipation	4	2	0	0
Anorexia	3	2	1	0
Nausea/vomiting	8	2	1	0
Dysgeusia	2	0	0	0
Fatigue	6	2	1	0
Skin rash	4	1	0	0
T-Bil	1	0	1	0
AST/ALT	1	1	0	0
Infection	0	1	3[a]	0
Febrile neutropaenia	0	0	0	0

a Three cases; two with pneumonitis and one with pleuritis.

interval: 17.1–58.3%) in per protocol sets. In level 2, the recommended dose, among 19 patients, seven had a partial response. The response was 36.8% (95% CI: 16.3–61.6%). One patient treated at level 1 for four cycles had a partial response.

The median follow-up period was 16 months (range, 7–32 months). The median overall survival time was 11.1 months (95% CI: 8.1–15.3 months) and the median progression-free survival time was 5.0 months (95% CI: 3.6–6.0 months) (Fig. 1A and B).

4. Discussion

Systemic chemotherapy for advanced stage NSCLC is regarded as palliative; therefore, the main purpose is to maintain quality of life during an extended survival period. The current standard chemotherapy for stage wet IIIB (a subgroup including patients with malignant effusion and/or no indications for radiation) or stage IV is platinum doublets.[5] Cisplatin combinations confer a survival advantage than carboplatin combinations, according to one meta-analysis[13]; however, the difference was minor. Cisplatin-containing regimens require hospitalisation because massive hydration is essential to preventing renal toxicity, and their use is often restricted by renal, neuropathic and emetogenic toxicities. Although, the combination of carboplatin and paclitaxel is unique and is the most frequently used regimen in the world, among the standard treatments for advanced NSCLC[14], the infusion time remains rather long and additional supportive treatments are needed to prevent allergic reactions.[15] Furthermore, peripheral neurotoxicity is occasionally problematic.

Many reports have suggested synergistic anti-tumour effects when platinum and fluoropyrimidines, including 5FU[16] and S-1[17], are used together. A recent randomised phase III trial in Japan[18] showed a combination of cisplatin with S-1 to be a feasible standard regimen for advanced gastric cancer. The combination of cisplatin and S-1 was also active in patients with NSCLC.[10] Thus, the combination of carboplatin plus S-1 is a potential regimen, possibly shortening hospitalisation as well as being convenient, if it can achieve activity equivalent to those of other standard platinum doublets.

Table 4 – Tumour response.

	Number of patients	Response				
		CR	PR	SD	PD	NE
Part of Phase I						
Level 1	3	0	1	1	1	0
Level 2	3	0	2	1	0	0
Level 3	6	0	0	4	0	2
Part of Phase II						
Level 2	16	0	5	9	2	0
Total	28	0	8	15	3	2

Response rate at the recommended dose: 36.8% (95% CI: 16.3–61.6%).
CR, complete response; PR, partial response; SD, stable disease, PD, progressive disease, NE, not evaluable.
Tumour responses were evaluated using RECIST criteria.

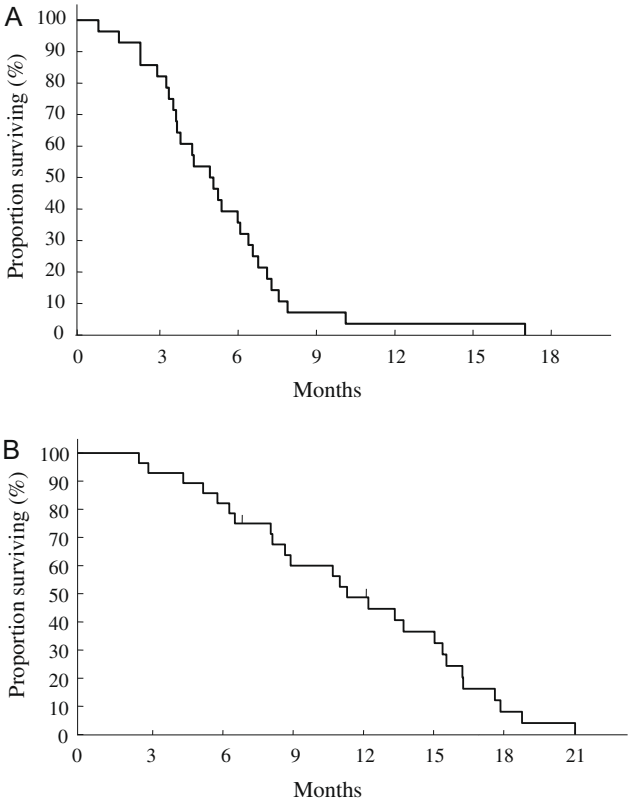

Fig. 1 – (A) Kaplan–Meier curve for progression-free survival (PFS) of all eligible patients (*n* = 28). Median PFS was 5.0 months (95% CI: 3.6–6.0 months). (B) Kaplan–Meier curve for overall survival. (OS) of all eligible patients (*n* = 28). Median OS was 11.1 months (95% CI: 8.1–15.3 months).

The RD of the combination was level 2 (AUC5 of CBDCA on day 1 and 80 mg/m^2 of S1 on days 1 to 14, every 3 weeks). This level was not found to be acceptable in a previous report by Kaira et al.[19] despite treatment every 4 weeks. One possible explanation is that they treated only three patients at this level and one was quite elderly, suggesting individual variation. We assessed 19 patients at level 2 in this study, and two (10.5%) had grade 4 thrombocytopaenia, while one (5%) had grade 4 anaemia. No patients experienced febrile neutropaenia, blood transfusion or bleeding, suggesting the safety of level 2. The DLT was the necessity of a delay exceeding 14 d in administration of the second course, due to thrombocytopaenia and neutropaenia, at level 3. However, the median interval until the course at level 2 was 22 (21–44) d, and the median number of treatment cycles was four (range 2–6), suggesting that the treatment schedule could be maintained in most cases. As to haematological toxicity, there were three grade 3 lung infections in two patients, but both recovered with antibiotic treatment were able to resume the chemotherapy. Overall, the incidence of adverse events at the RD appeared to be lower than that with the standard chemotherapy for NSCLC.

The response rate at the RD was 36.8%, i.e. equivalent to those of other standard platinum doublets. The median overall survival time was 11.1 months and the median progression-free survival time was 5.0 months. These rates were not inferior to those of carboplatin/paclitaxel regimens reported in either a western country[5] or Japan.[20]

In summary, to our knowledge, this is the first report on the RD for a carboplatin/S-1 combination administered with a 3-week cycle. Furthermore, its effectiveness in the phase II part of the trial was demonstrated. A randomised non-inferiority phase III trial comparing carboplatin/S-1 with carboplatin/paclitaxel in chemotherapy-naïve patients with NSCLC is currently underway. This combination is also considered to be an alternative therapy for elderly patients and those with poor PS.

Conflict of interest statement

None declared.

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REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;**58**:71–96.
2. Kubota K, Watanabe K, Kunitoh H, et al. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. *J Clin Oncol* 2004;**22**:254–61.
3. Le Chevalier T, Brisgand D, Douillard JY, et al. Randomised study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small cell lung cancer: Results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994;**12**:360–8.
4. Cardenal F, López-Cabrerizo MP, Antón A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 1999;**17**:12–8.
5. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 2002;**346**:92–8.
6. Shirasaka T, Shimamoto Y, Ohshimo H, et al. Department of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 1996;**7**:548–57.
7. Takechi T, Fujioka A, Matsushima E, Fukushima M. Enhancement of the antitumour activity of 5-fluorouracil (5-FU) by inhibiting dihydropyrimidine dehydrogenase activity (DPD) using 5-chloro-2, 4-dihydroxypyridine (CDHP) in human tumour cells. *Eur J Cancer* 2002;**38**:1271–7.
8. Takechi T, Nakano K, Uchida J, et al. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother Pharmacol* 1997;**39**:205–11.
9. Kawahara M, Furuse K, Segawa Y, et al. Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 2001;**85**:939–43.

10. Ichinose Y, Yoshimori K, Sakai H, et al. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004;**10**:7860–4.
11. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989;**7**:1748–56.
12. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;**92**:205–16.
13. Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004;**22**:3852–9.
14. Socinski MA, Crowell R, Hensing TE, et al. Treatment of non-small cell lung cancer, stage IV: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;**132**(Suppl. 3): 277S–289S.
15. Weiss RB, Donehower RC, Wiernik PH, et al. Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;**8**:1263–8.
16. Shirasaka T, Shimamoto Y, Ohshimo H, et al. Metabolic basis of the synergistic antitumor activities of 5-fluorouracil and cisplatin in rodent tumor models in vivo. *Cancer Chemother Pharmacol* 1993;**32**:167–72.
17. Sakaki E, Tominaga K, Kuwamura H, et al. Synergistic antitumor effect of combined 5-fluorouracil (5-FU) with 5-chloro-2, 4-dihydroxypyridine on 5-FU-resistant gastric cancer cells: possible role of a dihydropyrimidine dehydrogenase-independent mechanism. *J Gastroenterol* 2007;**4**:816–22.
18. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;**9**:215–21.
19. Kaira K, Sunaga N, Yanagitani N, et al. A phase I dose-escalation study of S-1 plus carboplatin in patients with advanced non-small-cell lung cancer. *Anticancer Drugs* 2007;**18**:471–6.
20. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;**18**:317–23.