A phase I dose-escalation study of S-1 plus carboplatin in patients with advanced non-small-cell lung cancer

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We conducted a phase I study to determine the maximum tolerated dose, the recommended dose and the safety profile of S-1 and carboplatin combination regimen in the treatment of patients with advanced non-small-cell lung cancer. Chemotherapy-naive patients with advanced non-small-cell lung cancer were treated with S-1 and carboplatin. S-1 was administered orally twice daily for 14 days and carboplatin on day 1 of each cycle, and this was repeated every 4 weeks. Doses of each drug were planned as follows: level 1, 5/65; level 2, 5/80; level 3, 6/80 [carboplatin (area under the curve, mg/ml/min)/S-1 (mg/m^2/day)]. The dose-limiting toxicity of the regimen was assessed during the first chemotherapy cycle. Twelve patients were enrolled in this study. The main grade 3 or grade 4 toxicities observed during the first cycle were neutropenia (41%), thrombocytopenia (41%) and transaminase elevation. Two of three patients in level 2 had dose-limiting toxicity and this level was considered the maximum tolerated dose. Level 1 was selected as the recommended dose. Objective responses were seen in four patients (response rate 33%). The combination of S-1 plus carboplatin is a feasible and well-tolerated regimen for the treatment of patients with advanced non-small-cell lung cancer. ***Anti-Cancer Drugs*** **18:471–476 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. Most patients present with locally advanced stage III or metastatic stage IV disease. A meta-analysis of 52 randomized trials indicated a significant, but modest survival advantage for patients treated with cisplatin-containing regimens, compared with best supportive care alone [1]. The recent introduction of newer agents, with improved response rates in NSCLC [1], offers hope for more active combination regimens. Although the current practice of treating patients with stage IV disease includes the addition of newer-generation agents such as vinorelbine, gemcitabine, paclitaxel or docetaxel to a platinum agent, no combination has emerged as a gold standard [1,2].

S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an oral anticancer agent comprised of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [3]. Tegafur, a prodrug of 5-fluorouracil (5-FU), is gradually converted to 5-FU and is rapidly catabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. 5-Chloro-2,4-dihydroxy pyridine is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting DPD [4]. When combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations, both in plasma and in tumors. In addition, it has been suggested that CDHP has the potential to enhance the antitumor activity of 5-FU against subcutaneous tumors in nude mice [5]. Oxo is an agent that decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase. Oxo preferentially localizes in the gut rather than in the tumor and has a potential biochemical effect on the enzyme pyrimidine phosphoribosyl transferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects [6].

In a phase II study of S-1, which was orally administered at approximately 40 mg/m^2 twice a day for 28 days followed by a 2-week rest period in 59 advanced NSCLC patients without prior chemotherapy, the response rate was 22% and the median survival time was 10.2 months. The incidence of grade 3 or grade 4 toxicity was low [7]. Additionally, a response rate of 47%, median survival time of 11 months and 1-year survival rate of 45% were

reported in the phase II study of 55 advanced NSCLC patients when S-1 was combined with cisplatin [8]. The patients in this study were treated with the oral administration of S-1 at 40 mg/m^2 twice a day for 21 consecutive days, whereas cisplatin (60 mg/m^2) was administered intravenously on day 8. This schedule was repeated every 5 weeks. Hematological toxicities of grades 3 and 4 included neutropenia (29%) and anemia (22%). No grade 4 nonhematological toxicity was observed and grade 3 toxicity included anorexia (13%), vomiting (7%) or diarrhea (7%).

Carboplatin, a less toxic analogue of cisplatin, is less nephrotoxic and less emetogenic than cisplatin, and has an antitumor activity similar to that of cisplatin [9,10]. Hydration is not required before or after treatment with carboplatin, which would make it suitable for use in the outpatient setting. Recently, Watanabe *et al.* [11] reported a phase I/II study of S-1 plus carboplatin as outpatient chemotherapy in recurrent and/or metastatic head and neck cancer. The incidence of grade 3 or grade 4 toxicity was low, and thrombocytopenia and leucopenia were most commonly found as hematological toxicities, which were manageable without hospitalization.

Against this background, we conducted a phase I study of S-1 plus carboplatin in patients with advanced NSCLC to determine the maximum tolerated dose (MTD) to be investigated further in a phase II study.

Patients and methods

Patient eligibility

Eligible patients were required to have the following characteristics: histologically and/or cytologically proven unresectable stage IIIB or stage IV NSCLC; no previous chemotherapy or radiotherapy; a performance status (PS) of 0–2 on the Eastern Cooperative Oncology Group; an age range from 20 to 74 years; a life expectancy of 12 weeks or more; adequate bone marrow reserve (leucocyte count $\geq$ 4000/mm^3, neutrophil count $\geq$ 2000/mm^3, platelet count $\geq$ 100 000/mm^3 and hemoglobin $\geq$ 10 g/dl); normal liver function [total serum bilirubin $\leq$ 1.5 mg/dl, and aspartate transaminase (AST) and alanine transaminase (ALT) less than twice the upper limit of the normal range]; and normal renal function (serum creatinine $\leq$ 1.5 mg/dl and creatinine clearance $\geq$ 60 ml/min). Patients with concomitant malignancy, central nervous system metastases, active infectious diseases or other serious medical problems were ineligible. The local ethics committee approved the study and written informed consent was obtained from all patients.

Clinical study design

S-1 capsule, in the form of a 20- or 25-mg capsule containing 20 or 25 mg tegafur, respectively, was provided by Taiho Pharmaceutical. S-1 was administered twice daily, after breakfast and dinner. S-1 was given for 14 consecutive days, followed by a 14-day rest period. The dose of S-1 was to be escalated in successive cohorts of new patients to 65 and 80 mg/m^2/day, the basis of on the patient's body surface area (BSA) as follows: at the dose level of 65 mg/m^2/day, BSA $<$ 1.25 m^2, 65 mg/day, BSA 1.25–1.5 m^2, 80 mg/day, and BSA $>$ 1.5 m^2, 100 mg/day at the dose level of 80 mg/m^2 day, BSA $<$ 1.25 m^2, 80 mg/day, BSA 1.25–1.5 m^2, 100 mg/day and BSA $>$ 1.5 m^2, 120 mg/day.

Carboplatin was dissolved in 500 ml of 0.9% saline solution and administered as a 90-min intravenous infusion on day 1 of the 14-day S-1 administration. Carboplatin was dosed using serum creatinine values and Calvert *et al.*'s [12] formula on the basis of a targeted area under the time–concentration curve (AUC). The starting dose was designated as 5.0 AUC values, which was planned to be increased to 6.0 AUC values. The prophylactic administration of granulocyte-colony stimulating factor (G-CSF) was not permitted. Administration of G-CSF was permitted in patients with grade 4 neutropenia and/or grade 3 febrile neutropenia. Subsequent courses of chemotherapy were initiated when the leucocyte counts were 4000/mm^3 or more and platelet counts were 100 000/mm^3 or more, after day 29. If the leucocyte or platelet counts had not returned to these levels by day 1 of the next course of chemotherapy, both drugs were withheld until full recovery. Treatment was carried out for at least two courses, unless unacceptable toxicity or disease progression occurred.

The planned dose levels are shown in Table 1. At least three patients were enrolled at each dose level. Initially, three patients were treated at dose level 1 and no intrapatient dose escalation was allowed. If one DLT was observed in the first three patients, three more patients were entered at this dose level, and dose escalation continued to the next level if fewer than three out of six patients experienced DLT during the first one cycle. The MTD was defined as the previous level from the level at which DLT was observed in two out of three or in three out of six patients during the first one cycle. If all three patients experienced a DLT at level 1, a dose reduction to level 0 was planned. DLT was defined as follows: (1) grade $\geq$ 3 nonhematological toxicities, except nausea/vomiting, (2) grade 4 thrombocytopenia, (3) grade 4 neutropenia, (4) febrile neutropenia during the first cycle, (5) any

Table 1 Planned dose of each level

Level	Carboplatin (AUC)	S-1 (mg/m^2)	Enrolled patients
0	4	65	
1[a]	5	65	9
2	5	80	3
3	6	80	

AUC, area under the curve.
[a]Starting dose.

unresolved toxicity, requiring a delay in the administration of a subsequent course exceeding 8 days and (6) any grade 2 toxicity which, in the judgement of the investigator, required dose reduction or discontinuation of therapy. Toxicities were assessed according to Common Terminology Criteria for Adverse Events version 3.0. Second-line chemotherapy or other treatments after this study were not prohibited by the protocol.

Treatment assessment

Patients were evaluated before treatment with a complete blood cell count, a differential count, routine chemistry measurements, a chest radiograph, a chest computed tomographic (CT) scan, an abdominal CT scan, whole-brain magnetic resonance imaging or CT scan and an isotope bone scan. Evaluations performed weekly were complete blood cell count, differential count, routine chemistry measurements, physical examination and toxicity assessment. We used the Response Evaluation Criteria in Solid Tumors to assess response to S-1 plus carboplatin [13]. Response based on target (and nontarget lesions) was defined as follows: complete response (CR), disappearance of all target (nontarget) lesions; partial response (PR), 30% or more reduction in size (or disappearance of one or more nontarget lesions); stable disease (SD), less than 30% decrease and less than 20% increase in size (or the persistence of one or more nontarget lesions); progressive disease (PD), more than 20% increase in size (or the appearance of new nontarget lesions and/or progression of existing nontarget lesions). The overall response was defined as the best response recorded from the start of treatment until disease progression or recurrence, confirmed by repeated assessments performed no less than 4 weeks after the criteria for response were first met.

Results

Patient characteristics

Between October 2005 and June 2006, 12 patients were enrolled in this study and the clinical characteristics are summarized in Table 2. The number of patients entered at each level is listed in Table 1. The median age of the patients was 64 years (range, 39–74 years). Six patients were men and six were women. PS, clinical stage and histology of the patients were as follows: three patients with PS 0, nine patients with PS 1; no patients with stage IIIB, 12 patients with stage IV; eight patients with adenocarcinoma, four patients with squamous cell carcinoma.

Table 2 Patient characteristics

Characteristic	No. of patients
Patients enrolled	12
Age (years)	
Median	64
Range	39–74
Sex	
Male	6
Female	6
Performance status (Eastern Cooperative Oncology Group)	
0	3
1	9
Histology	
Adenocarcinoma	8
Squamous cell carcinoma	4
Stage	
IIIB	0
IV	12
Prior treatment	
None	12
Surgery	0

Toxicity

Toxicity was evaluated in all treated patients. The number of patients who developed DLT in the first cycle at each level is listed in Table 3. At level 1, one patient (patient 2) developed grade 4 thrombocytopenia. Therefore, three more patients were added at this dose level and one patient (patient 4) developed a delay in the administration of a subsequent course exceeding 8 days. The patient developed grade 2 fever and grade 2 infection on day 16. Moreover, grade 3 neutropenia and grade 3 thrombocytopenia occurred on day 20 and 17, respectively. As the hematological toxicities resolved on day 39, the administration of the next course was started on day 40. Two patients out of six developed DLT at level 1 and three patients were started at level 2. At this dose level, one patient (patient 11) developed grade 4 thrombocytopenia and grade 4 neutropenia. The grade 4 thrombocytopenia and grade 4 neutropenia occurred on day 21. One more patient (patient 12) developed grade 4 thrombocytopenia, grade 3 neutropenia and grade 3 transaminase elevation. Grade 4 thrombocytopenia occurred on day 16 and grade 3 transaminase elevation on day 3. The patient improved without intervention. Thus, two patients out of three developed DLT at level 2. To check the safety of the dose at level 1, however, three more patients were added at this dose level and one patient (patient 7) had a delay in the administration of a subsequent course exceeding 8 days. The patient developed grade 3 neutropenia and grade 3 thrombocytopenia on day 24. As the hematological toxicities resolved on day 40, the administration of subsequent course was started on day 41. Thus, in total, three patients out of nine developed DLT at level 1. No pulmonary toxicities such as interstitial pneumonia and treatment-related deaths were observed at either level. No grade 3 or 4 fatigue or asthenia were observed.

We concluded that the MTD was level 2, carboplatin AUC 5 on day 1, and S-1 80 mg/m^2 for 14 consecutive days, followed by a 14-day rest period and the recommended dose for the phase II study was level 1, carboplatin AUC 5 on day 1 and S-1 65 mg/m^2 for 14 consecutive days, followed by a 14-day rest period. The hematological and nonhematological toxicities are listed in Table 3.

Table 3 Haematological and nonhaematological toxicities

Patient no.	Haematological toxicities (CTCAE grade)						Non-haematological toxicities (CTCAE grade)		Delay	DLT
	Age	Sex	Neut	Hb	Plt	FN	<Grade 2	>Grade 3		
Level 1										
1	63	F	0	0	0	0	none	none	none	none
2	55	F	0	1	4	0	appetite loss (1)	none	none	yes
3	56	F	0	0	0	0	appetite loss (1), nausea (1)	none	none	none
4	64	F	3	1	3	0	appetite loss (1), nausea (1), fatigue (1), fever (2), infection (2)	none	yes	yes
5	64	F	0	0	1	0	none	none	none	none
6	57	M	0	0	0	0	none	none	none	none
7	71	M	3	0	3	0	appetite loss (1), nausea (1)	none	yes	yes
8	64	M	0	0	2	0	appetite loss (1), AST/ALT (1)	none	none	none
9	74	M	3	0	2	0	appetite loss (1), nausea (1)	none	none	none
Level 2										
10	69	M	2	0	1	0	skin rash (2)	none	none	none
11	39	F	4	1	4	0	appetite loss (1), nausea (1)	none	none	yes
12	74	M	3	0	4	0	none	AST/ALT (3)	none	yes

AST, aspartate transaminase; ALT, alanine transaminase; CTCAE, common terminology Criteria for adverse events; Delay, delay in the administration of a subsequent course exceeding 8 days; DLT, dose-limiting toxicity; FN, febrile neutropenia; Hb, anemia; Neut, neutropenia; Plt, thrombocytopenia.

Table 4 Treatment cycles and tumour response

Patient	Treatment cycles	Response
1	1	PD
2	4	PR
3	2	SD
4	3	PR
5	4	SD
6	1	PD
7	4	SD
8	4	PR
9	4	PR
10	3	SD
11	3	SD
12	1	SD
	Median cycles	Response rate
	3	33%

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

Response rate

Twelve patients were assessable for response to treatment (Table 4). A PR was observed in four cases. The overall response rate was 33%. In the dose escalation levels, four of nine patients in level 1 achieved a partial response.

Discussion

This is the first report of a phase I study designed to determine the DLT and MTD of S-1 plus carboplatin for the treatment of chemotherapy-naive patients with advanced NSCLC. At level 2, four dose-limiting events occurred in two out of three patients, indicating that the MTD had been reached. Therefore, the MTD of the combination was defined at dose level 2, i.e. S-1 80 mg/m^2 and carboplatin AUC 5. All enrolled patients (12) were evaluated for efficacy and toxicity. Four PRs were seen, with an overall response rate of 33%. Hematological toxicities were mild in our study. Grade 3 or grade 4 neutropenia occurred in 41% of patients; three of nine patients in level 1 and two of three patients in level 2. No febrile neutropenia was detected. Grade 3 or grade 4 thrombocytopenia was observed in five patients (41%). Nonhematologic toxicities were also mild. Although grade 3 transaminase elevation was observed in one patient, the patient improved without intervention. No other patient experienced grade 3 or grade 4 nonhematological toxicities. Two patients experienced hematological toxicity requiring a delay in the administration of a subsequent course exceeding 8 days.

S-1 is a novel anticancer drug and the regimen of S-1 combined with cisplatin has been examined in advanced NSCLC [8]. The standard chemotherapy regimen for NSCLC is considered to be a platinum-based two-drug combination chemotherapy that uses paclitaxel, gemicitabine, docetaxel or vinorelbine. The median survival and the response rate in the recent phase III trials that use these combination chemotherapies have been reported to be 7–9 months and 17–28%, respectively. Grade 3 or grade 4 hematological and nonhematological toxicities were observed in 57–76% (neutropenia) and 4–35% (vomiting), respectively [9,13]. Ichinose *et al.* [8] reported that S-1 plus cisplatin combination chemotherapy showed a promising effectiveness with acceptable toxicity rates in NSCLC patients and the incidence of the toxicities seemed to be lower than these phase III trials. Recently, Hotta *et al.* [14] in a meta-analysis of randomized clinical trials described that combination chemotherapy consisting of cisplatin plus a new agent produced a significant survival advantage compared with that of carboplatin plus the same new agent. According to the result of their meta-analysis, patients on cisplatin-based chemotherapy frequently developed nausea and vomiting, and thrombocytopenia was more frequently during carboplatin-based chemotherapy. It is, however, still not known whether cisplatin is superior to carboplatin in S-1 combination chemotherapy.

The combination of a platinum compound and 5-FU has been proven to have synergic antitumor effect in many experimental and clinical studies [15,16]. The mechanism of the synergism of these two agents remains unclear, although there are various hypotheses concerning the modulatory effect of platinum compounds on 5-FU. It has been suggested that the platinum-induced intracellular folate level potentiates the effect of 5-fluorodeoxyuridine monophosphate by forming a covalent ternary complex with thymidylate synthase, leading to enhanced 5-FU cytotoxicity [17]. Yoshizawa *et al.* [18] reported that a combination of carboplatin and 5-FU was promising and showed acceptable toxicity in NSCLC patients. The results of a 5-FU trial also demonstrated that a combination of carboplatin and 5-FU was effective and tolerable in patients with head and neck cancer [19]. Oral S-1 administration, however, generates a higher concentration of 5-FU than protracted intravenous injection of 5-FU given in a dose equimolar to the tegafur in S-1, whereas the incidence of adverse events concerning the gastrointestinal tract does not increase [20,21]. Thus, we must examine whether a combination of platinum compound and S-1 is effective and tolerable in advanced NSCLC. To the best of our knowledge, a combination of S-1 plus carboplatin has not been described previously in patients with advanced NSCLC.

In this study with S-1, the treatment modality was determined on the basis of the phase II trial of S-1 plus cisplatin in patients with advanced NSCLC [8] and a phase I/II study of S-1 combined with carboplatin in recurrent and/or metastatic head and neck cancer [11]. In this phase II study of S-1 plus cisplatin [8], the schedule of cisplatin 60 mg/m^2 on day 8 and S-1 40 mg/m^2 twice a day from day 1 for 3 weeks was repeated every 5 weeks. According to the phase I/II trial of S-1 plus cisplatin in patients with advanced gastric cancer [22], the dose of cisplatin was decreased from 80 to 60 mg/m^2 and the cisplatin was administered every 5 weeks other than 3 or 4 weeks. In a phase I/II study of S-1 plus carboplatin [11], the schedule of carboplatin AUC 2.5 on day 8 and S-1 of a fixed dose of 40, 50 or 60 mg twice daily on the basis of the patient's BSA from day 1 for 3 weeks was repeated every 5 weeks. These trials used combination chemotherapy of platinum on day 8 and S-1 from day 1 for 21 days followed by a 14-day rest. The recent phase III trials in NSCLC, however, use the combination chemotherapy of platinum on day 1 and new agents every 3 or 4 weeks [9,23]. The combination chemotherapy of S-1 plus carboplatin should be examined in advanced NSCLC patients.

Therefore, we planned to administer carboplatin on day 1 rather than on day 8. When S-1 is administered from day 1 for 21 days followed by a 14-day rest, the course count is of 5 weeks and it is then repeated. As the administration of platinum in NSCLC is generally repeated every 3 or 4 weeks [9,23], we planned that S-1 would be administered for 14 days followed by a 14-day rest and the schedule was repeated every 4 weeks. As the recommended dose of S-1 was 80 mg/m^2/day in advanced NSCLC, 65 mg/m^2/day which is a lower dose than 80 mg/m^2/day, was selected as the strating dose. Carboplatin was administered at a fixed dose of AUC 5. In this study, the incidence of thrombocytopenia was higher; however, nonhematological toxicities were lower than in the study of S-1 plus cisplatin in NSCLC. Moreover, the incidence of the toxicities was lower than in recent phase III trials [9].

In conclusion, the results of this study indicate that the combination of S-1 plus carboplatin is a safe and well-tolerated regimen in patients with advanced NSCLC. The optimal dosage schedule for a phase II study is carboplatin AUC 5 on day 1 and S-1 65 mg/m^2 for 14 consecutive days, followed by a 14-day rest period. A multicenter phase II trial is already being done, to further evaluate the efficacy and the toxicity of this regimen.

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