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ORIGINAL ARTICLE

A phase II study of S-1 monotherapy as second-line treatment for advanced non-small cell lung cancer

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Abstract
Purpose To assess the efficacy and toxicity of an oral anticancer fluoropyrimidine derivative, S-1, for previously treated patients with advanced non-small cell lung cancer (NSCLC).
Patients and methods Patients with advanced (clinical stage IIIB-IV) NSCLC who had previously received one platinum-based chemotherapy were enrolled. S-1 was administered orally at the dosage decided by using the nomogram based on patient BSA b.i.d. for 28 consecutive days, repeated every 6 weeks.
Results Between August 2005 and July 2007, 50 patients were entered into this study. Six patients achieved partial response (PR), and the overall response rate of eligible patients was 12.5% (6/48) (95% confidence interval (95%CI), 3.1–21.9%). Disease control rate was 39.6% (19/48) (95%CI, 25.7–53.4%). Median progression-free survival was 2.5 months. Median survival time was 8.2 months, and 1-year survival rate was 29.6%. No grade 4 toxicities were encountered. Grade 3 hematological toxicities comprised neutropenia in one patient (2.1%) and anemia in one patient (2.1%). Grade 3 non-hematological toxicities were observed in only five patients (10.4%). Treatment-related death did not occur.
Conclusion S-1 is an active and well-tolerated monotherapy for second-line treatment of advanced NSCLC.

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Keywords Non-small cell lung cancer (NSCLC) · Second-line chemotherapy · S-1 · Oral cytotoxic agent

Introduction

Lung cancer is the leading cause of cancer death in many countries [1]. Approximately 80% of lung cancers result from the non-small cell histology, and most patients show locally advanced stage III or metastatic stage IV disease at diagnosis. Advanced non-small cell lung cancer (NSCLC) continues to display poor outcomes, with a response rate of 17–32%, median survival time (MST) of 7.4–10.0 months, and a 1-year survival rate of 31–43% in patients receiving standard two-drug chemotherapy regimens [2, 3]. Almost all patients treated with first-line chemotherapy experience disease progression. The results of phase III clinical trials indicate single-agent chemotherapy with docetaxel, pemetrexed or erlotinib as the standard chemotherapy regimen for recurrent NSCLC [4–7].

S-1 is a novel oral fluoropyrimidine derivative consisting of tegafur and two modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate, in a molar ratio of 1:0.4:1 [8]. Tegafur is a prodrug of 5-fluorouracil (5-FU). CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase, an enzyme for 5-FU degradation. CDHP with tegafur is thus expected to yield prolonged 5-FU concentrations in serum and tumor tissue. Potassium oxonate is a reversible competitive inhibitor of orotate phosphoribosyltransferase, an enzyme for 5-FU phosphoribosylation in the gastrointestinal (GI) mucosa. Potassium oxonate reportedly ameliorates the GI toxicity of tegafur by decreasing 5-fluorodeoxyuridine monophosphate production in the GI mucosa [9].

A phase II clinical trial of S-1 monotherapy for chemonaïve patients with advanced NSCLC was conducted in Japan [10]. The response rate was 22.0% and MST was 10.2 months. The only hematological grade 4 toxicity observed was neutropenia in 1 patient (1.7%), and no non-hematological grade 4 toxicities were observed. Response rates to third-generation agents (i.e., paclitaxel, docetaxel, vinorelbine and gemcitabine) used as monotherapy to treat chemotherapy-naïve NSCLC have been reported as 13–20% [11]. These results indicate that S-1 may offer an active agent for patients with advanced NSCLC. The oral formulation and low incidence of adverse reactions permit treatment on an outpatient basis. Against this background, we conducted a phase II trial of S-1 monotherapy as second-line treatment in patients with advanced NSCLC.

Patients and methods

Patient eligibility

Patients were required to have histological or cytological proof of stage IIIB (without indication for radiotherapy) or stage IV NSCLC that had progressed after administration of one platinum-based chemotherapy regimen. Eligibility criteria were as follows: measurable lesions; life expectancy $\geq$3 months; age range of 20–80 years; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2; adequate bone marrow reserved (defined as absolute granulocyte count $\geq$2,000/ml and platelet count $\geq$100,000/ml); adequate hepatic and renal function (defined as serum creatinine level $\leq$1.1 mg/dl, both AST and ALT $\leq$ 100 IU/l and total bilirubin $\leq$ 1.5 mg/dl); and partial pressure of arterial oxygen >70 Torr Exclusion criteria included pregnancy, serious concomitant diseases (active infection, severe heart disease or uncontrolled diabetes mellitus), concomitant malignancy, pleural effusion necessitating treatment, symptomatic cerebral involvement, obvious interstitial pneumonia or pulmonary fibrosis on chest radiography. Written informed consent was required from all patients. The Ethics Committee of Fujita Health University Hospital approved this study protocol.

Treatment schedule

Based on two clinical trials in patients with advanced NSCLC [10, 12], S-1 was administered orally for 28 consecutive days followed by a 2-week rest period. Three dosages of S-1 were selected according to body surface area (BSA): BSA < 1.25 m^2, 40 mg b.i.d.; BSA $\geq$ 1.25 m^2 but < 1.5 m^2, 50 mg b.i.d.; and BSA $\geq$ 1.5 m^2, 60 mg b.i.d. The cycle was repeated unless unacceptable toxicity or disease progression occurred. Drug doses were adjusted according to hematological and non-hematological toxicities. The dose was reduced by one level (20 mg/day) in patients with BSA $\geq$ 1.25 m^2 and evidence of grade 3 or more hematological toxicity (leukocytes < 2000/μl, granulocytes < 1,000/μl or platelet count < 50,000/μl) or grade 2 or more non-hematological toxicity (except alopecia or anorexia) during any cycle of administration. If recovery from such toxicities was confirmed at the reduced dose, administration was continued at that reduced dose. If a patient with BSA < 1.25 m^2 experienced the above toxicities, no further treatment with S-1 was administered. If a rest period of >4 weeks was required, the patient was withdrawn from the study. Antiemetic drugs were not administered prophylactically.

Evaluation of responses and toxicity

Pretreatment evaluation included medical history, physical examination, complete blood count, bone marrow examination, serum biochemical analyses, chest radiography, electrocardiography and urinalysis. All patients underwent radionuclide bone scan, magnetic resonance imaging or computed tomography (CT) of the brain, and CT of the thorax and abdomen. Complete blood count, biochemical tests, serum electrolytes, urinalysis and chest radiography were obtained before administration of chemotherapy.

Responses and toxicity were evaluated on the basis of tumor images obtained by CT and other techniques, laboratory data and symptoms and signs before, during and after administration of the study drugs and during the period from completion of treatment to the final analysis. The baseline radiographic evaluations are carried out within 4 weeks before administration of chemotherapy. Measurable disease parameters were determined by various means such as CT. In this time, the evaluations were assessed every 4 weeks, because the trial of tri-weekly docetaxel as second-line treatment for advanced NSCLC was assessed every 4 weeks [13]. Target response rate in our study was based on the response rate of that study. Evaluations were performed in compliance with the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for antitumor activity and with Common Terminology Criteria for Adverse Events version 3.0 for safety. Patients were withdrawn from the study if evidence of tumor progression was obtained.

The primary endpoint of this study was the response rate. A standard two-stage Simon design was employed. A response rate of 5.0% precluded further study, whereas a response rate of 18.2% (response rate of docetaxel in patients with recurrent NSCLC [13]) would indicate that further study is warranted (i.e., $P_0 = 0.05$ and $P_1 = 0.182$ in Simon terminology). Using α and β errors of 0.05 and 0.20, respectively, 17 patients were enrolled in the first stage, and

if ≤1 response was observed, the trial was to be terminated. Otherwise, an additional 27 patient were to be enrolled, and if ≤4 responses were observed in 44 patients, the agent would not be considered worthy of further study. If ≥5 responses were observed, the drug would be considered sufficiently active to warrant further study. Considering the percentage of probable dropout cases, 50 patients were required. Secondary endpoints were toxicity, progression-free survival (PFS) and overall survival. Overall survival was assessed from the start of this treatment to death from any cause. PFS was defined as the time from the start of this treatment to the earliest occurrence of disease progression or death from any cause. Overall survival and PFS were calculated according to the Kaplan–Meier methods.

Results

Patient characteristics

A total of 50 patients were enrolled in this study between August 2005 and July 2007. Two patients were excluded as ineligible, because they had diffuse pulmonary fibrosis. No grade 3/4 toxicities occurred in them. As a result, 48 patients (36 men, 12 women) were assessable for toxicity, response and survival. Characteristics of these 48 patients are listed in Table 1. Median age was 66.5 years. ECOG performance status was 2 in 12 patients (25%) and stage IV disease was identified in 38 patients (79%) patients. The predominant histological type was adenocarcinoma (75%). All 48 patients had received only one prior platinum-based chemotherapeutic regimen. Of the 48 patients, 19 had initially responded to platinum-based therapy, 24 patients had achieved stable disease (SD), and 5 patients had progressive disease (PD).

Table 1 Patient characteristics ($n = 48$)

Characteristics	
Male/female	36/12
Median age, years (range)	66.5 (52–79)
Performance status	
0	1
1	35
2	12
Stage	
IIIB	10
IV	38
Histology	
Adenocarcinoma	36
Squamous cell carcinoma	5
Other	7
Prior chemotherapy	
Carboplatin/paclitaxel	45
Carboplatin/docetaxel	2
Carboplatin/vinorelbine	1
Response to prior chemotherapy	
Partial response	19
Stable disease	24
Progressive disease	5

Efficacy of treatment

Partial response was identified in 6 patients. Overall response rate was 12.5% (6/48) (95% confidence interval (95%CI), 3.1–21.9%). SD was achieved in 13 patients (27.1%), and 29 patients (60.4%) showed PD. Disease control rate was 39.6% (19/48) (95%CI, 25.7–53.4%). The median response duration was 7.8 months (range, 3.5–28.3 months. All 48 patients were included in the survival analysis, with a median follow-up time of 8.6 months. Median progression-free survival was 2.5 months. Overall MST was 8.2 months, and the 1-year survival rate was 29.6% (Fig. 1).

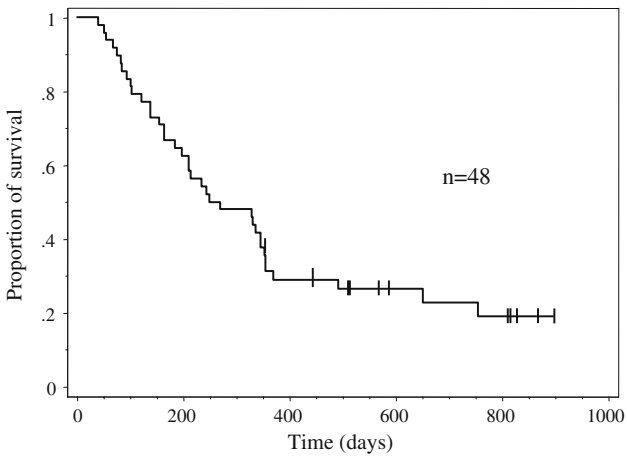

Fig. 1 Kaplan–Meier estimated overall survival curves. Median survival time, 8.2 months; 1-year survival rate, 29.6%

Toxicities

The major toxicities encountered during the study period are shown in Table 2. Incidences of toxicities were evaluated in 48 eligible patients. Both hematological and non-hematological toxicities were mild, and no grade 4 toxicities developed. Grade 3 hematological toxicities comprised neutropenia in one patient (2.1%) and anemia in one patient (2.1%). Grade 3 non-hematological toxicities were anorexia in one patient (2.1%), rash in one patient (2.1%), infection in two patients (4.2%), and peripheral neuropathy in one patient (2.1%). All of these toxicities were manageable, and the patients recovered when drug

Table 2 Toxicity ($n = 48$)

Toxicity	Grade				Grade 3–4%
	1	2	3	4	
Hematological					
Leukopenia	5	2	0	0	
Neutropenia	4	2	1	0	2.1
Thrombocytopenia	7	2	0	0	
Anemia	9	1	1	0	2.1
Non-hematological					
Anorexia	12	5	1	0	2.1
Vomiting	0	2	0	0	
Diarrhea	3	1	0	0	
Rash	0	1	1	0	2.1
Infection	-	0	2	0	4.2
Infection with G3/4 neutrophils	-	0	0	0	
Elevated transaminases	2	2	0	0	
Elevated total bilirubin	4	0	0	0	
Peripheral neuropathy	0	0	1	0	2.1
Alopecia	1	0	-	-	
Pigmentation	5	3	-	-	

administration was interrupted. No treatment-related deaths were observed.

Administration

A total of 138 cycles were administered to 48 patients. The median number of cycles administered per patient was 2 (range, 1–21). The dose was reduced in ten patients due to toxicities, as follows: grade 3 neutropenia, $n = 1$; grade 2–3 anorexia, $n = 3$; grade 3 rash, $n = 1$; grade 3 infection, $n = 2$; grade 2 elevation of transaminases, $n = 2$; and grade 2 diarrhea, $n = 1$. Only 1 cycle of chemotherapy was administered in 20 patients, while 28 patients received ≥ 2 cycles. The reasons for only 1 cycle of treatment were PD in 14 patients and toxicities in 6 patients (grade 2–3 anorexia, $n = 5$; grade 3 neuropathy, $n = 1$).

Discussion

The standard second line-treatment for NSCLC is single-agent chemotherapy with docetaxel, pemetrexed or erlotinib [4–7]. Shepherd et al. [4] reported that second-line single agent treatment with docetaxel, at 75 mg/m^2 every 3 weeks, provided limited but significant survival benefits that outweighed treatment risks when compared to the best supportive care. Docetaxel has also demonstrated superiority in the second-line when compared to other single agent treatments such as vinorelbine or ifosfamide [5], but pemetrexed monotherapy as a second-line agent has recently demonstrated response rates and survival similar to those for docetaxel monotherapy [6]. The BR21 trial compared erlotinib, an oral epidermal growth factor receptor inhibitor, with the best supportive care in previously treated patients with NSCLC, showing a significant survival benefit with erlotinib treatment [7].

A phase II trial of S-1 monotherapy in chemotherapy-naïve patients with advanced NSCLC showed a response rate of 22% and an MST of 10.2 months [10]. Incidences of severe hematological and non-hematological toxicities were relatively low. Ichinose et al. [14] reported a phase II clinical trial of combination chemotherapy using S-1 and cisplatin in patients with previously untreated advanced NSCLC. This trial showed a 47% response rate and an MST of 11 months. These effects were comparable to those of third-generation chemotherapeutic agents such as paclitaxel, docetaxel, vinorelbine and gemcitabine. The oral formulation and low incidence of adverse reactions permit treatment on an outpatient basis. These findings indicate that S-1 monotherapy may offer a suitable second-line chemotherapy for advanced NSCLC.

This is the first phase II study designed to explore the efficacy and safety of single agent S-1 for second-line treatment of patients with advanced NSCLC. In this study, S-1 monotherapy showed an overall response rate of 12.5% and an MST of 8.2 months. No grade 4 toxicities were identified. Grade 3 hematological toxicities consisted of neutropenia in one patient (2.1%) and anemia in one patient (2.1%). Grade 3 non-hematological toxicities were observed in only five patients (10.4%), and no treatment-related deaths occurred. Currently, standard cytotoxic agents for second-line treatment are docetaxel and pemetrexed. Response rates reported for theses agents are 5.5–9.1%, with MSTs of 5.7–8.3 months [4–6]. In the present study with single agent S-1, the effects seem similar to those of standard agents. While efficacy appears to resemble that of two standard cytotoxic agents, significant differences exist in the toxicity profiles. The safety profile of pemetrexed was significantly better than that of docetaxel [6]. Patients treated with docetaxel were more likely to experience grade 3–4 neutropenia (40.2 vs. 5.3%; $P < 0.001$), febrile neutropenia (12.7 vs. 1.9%; $P < 0.001$) and infections associated with neutropenia (3.3 vs. 0%; $P = 0.004$) compared to patients treated using pemetrexed. S-1 monotherapy had an apparently lower rate of severe adverse events compared with that of docetaxel, and a similar rate of grade 3 or 4 hematological toxicities compared to that of pemetrexed [4–6].

Standard cytotoxic agents, docetaxel and pemetrexed, are intravenously administered. Recently, several clinical trials of oral cytotoxic agent (e.g., oral vinorelbine [11], oral topotecan [15] and oral taxane anticancer agent [16])

monotherapy for previously treated advanced NSCLC have been performed. These oral cytotoxic agents showed response rates of 0–5.6% and MSTs of 120 days to 27.9 weeks. In our trial, S-1 had a higher response rate and similar or longer survival time compared with those of these oral agents.

In conclusion, this phase II study demonstrates that oral S-1 monotherapy is active and well tolerated as a second-line chemotherapy in patients with advanced NSCLC. S-1 monotherapy could represent an appropriate treatment for patients failing to achieve response with first-line platinum-based regimens. Further investigations with a larger population are required to confirm our results.

Conflict of interest statement None.

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