S-1 Plus Cisplatin Combination Chemotherapy in Patients with Advanced Non–Small Cell Lung Cancer: A Multi-Institutional Phase II Trial

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ABSTRACT

Purpose: To evaluate the efficacy and toxicity of a novel combination chemotherapeutic regimen including cisplatin with an oral抗癌 agent, S-1 that consisted of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, for non–small-cell lung cancer (NSCLC) patients.

Experimental Design: In this phase II trial, patients with locally advanced and metastatic NSCLC were treated with the oral administration of S-1 at 40 mg/m2 twice a day for 21 consecutive days while cisplatin (60 mg/m2) was administered intravenously on day 8. This schedule was repeated every 5 weeks.

Results: Of 56 patients enrolled in the study, 55 patients were eligible and analyzed. The median number of cycles administered was 3 (range, 1–12 cycles). Among these 55 patients, one complete response and 25 partial responses were observed with an overall response rate of 47% (95% confidence interval, 34–61%). The median survival time was 10.2 months. As expected, the incidence of grade 3 was 22% [95% confidence interval (CI), 12–35%] and the incidence of grade 3 was 10% in anorexia, 8% in diarrhea, and 2% in stomatitis whereas no grade 4 nonhematologic adverse events were observed. Grade 3 toxicity included anorexia (13%), vomiting (7%), or diarrhea (7%).

Conclusions: S-1 plus cisplatin combination chemotherapy showed a promising effectiveness with acceptable toxicity rates in patients with advanced NSCLC. These results warrant further investigations of this regimen including a randomized controlled trial for its use as a first line treatment for NSCLC.

INTRODUCTION

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral anticancer agent comprised of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, in a molar ratio of 1:0.4:1 (1). Tegafur is a prodrug that generates 5-fruorouracil (5-FU) in the blood primarily via metabolism by liver enzyme cytochrome P450. 5-Chloro-2, 4-dihydroxypyridine enhances the serum 5-FU concentration by the competitive inhibition of dihydropyrimidine dehydrogenase, an enzyme responsible for 5-FU catabolism. The inhibitory effect of 5-chloro-2, 4-dihydroxypyridine on dihydropyrimidine dehydrogenase in vitro is reported to be 180 times higher than that of uracil (2). Potassium oxonate is a reversible competitive inhibitor of orotate phosphoribosyl transferase, a phosphoenzyme for 5-FU. Diarrhea induced by 5-FU administration is thought to be attributable to the phosphorylation of 5-FU by the enzyme in the gastrointestinal tissue. After the oral administration of potassium oxonate, the concentration of potassium oxonate in the gastrointestinal tissue is high enough to inhibit the enzyme, and the concentration in blood and tumor is reported to be either slight or nil (3). Because of these mechanisms, oral S-1 administration 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 (4, 5).

In a phase II trial of S-1, which was orally administered at approximately 40 mg/m2 twice a day for 28 days followed by a 2-week rest period in 59 advanced non–small-cell lung cancer (NSCLC) patients without prior chemotherapy, the response rate was 22% [95% confidence interval (CI), 12–35%] and the median survival time was 10.2 months. As expected, the incidence of severe gastrointestinal adverse events was low: i.e., the incidence of grade 3 was 10% in anorexia, 8% in diarrhea, and 2% in stomatitis whereas no grade 4 nonhematologic adverse events were observed. In addition, there were few severe hematologic adverse events. The incidence of grade 3 or 4 was 7% in neutropenia, 2% in anemia, and 2% in thrombocytopenia (6).

UFT is another dihydropyrimidine dehydrogenase-inhibitory fluoropyrimidine consisting of tegafur and uracil in a 1:4 molar concentration (7). UFT has a similar profile of adverse events but a weaker antitumor activity against NSCLC than S-1 (8). However, combination chemotherapy consisting of a daily

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Note: additional participating institutions and principal investigators included National Shikoku Cancer Center Hospital (Yoshihiko Segawa), Jizankai Tsuboi Hospital (Koichi Hasegawa), Niigata Cancer Center Hospital (Akira Yokoyama), and Nippon Medical School (Akinobu Yoshinura).

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administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin at mid-cycle of administration of UFT for advanced non–small-cell lung cancer yields a response rate of 29 to 38% and a median survival time of 10 to 13 months (9–11).

With these backgrounds, we conducted a phase II trial combining the oral administration of S-1 for 21 days and a bolus injection of cisplatin on day 8 in patients with advanced NSCLC.

PATIENTS AND METHODS

Patient Eligibility. The patients were eligible for this phase II trial if they had been either cytologically or histologically confirmed to have NSCLC; stage IIIB without any indications for radiotherapy or stage IV; measurable disease; no prior treatment; an age range from 20 to 74 years; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and a projected life expectancy of at least 3 months. Other eligibility criteria for an organ function were as follows: a leukocyte count of 4,000 to 12,000/μL; platelet count ≥100,000/μL; hemoglobin level of ≥9 g/dL; a serum bilirubin level <1.5 mg/dL; serum aspartate aminotransferase and alanine aminotransferase levels <100 IUL; alkaline phosphatase level of twice the upper limit or less; normal creatinine level; creatinine clearance rate of at least 60 mL/minute; partial pressure of arterial oxygen >70 Torr. For staging, all patients underwent a computed tomography scan of the thorax, including upper abdomen, and either a brain computed tomography scan or magnetic resonance images of brain, and a radioisotopic bone scan was also done in almost all patients.

Any patients who were pregnant or had concomitant serious diseases, a concomitant malignancy, pleural effusion necessitating treatment, or symptomatic cerebral involvement were excluded from the study. Written informed consent was required from all patients, and the protocol was approved by the institutional ethics committee of each of the participating institutions. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Tokyo Cooperative Oncology Group (Tokyo).

Treatment Schedule. S-1 capsule in the form of a 20 and 25 mg capsule containing 20 and 25 mg tegafur, respectively, was provided by the Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). S-1 was administered orally, 40 mg/m² twice a day, after meals between days 1 and 21. The actual dose of S-1 was selected as follows: in a patient with body surface area (BSA) < 1.25 m², 40 mg twice a day; BSA of 1.25 m² but <1.5 m², 50 mg twice a day; and BSA ≥ 1.5 m², 60 mg twice a day. Cisplatin (60 mg/m²) was administered intravenously on day 8 when patients were hydrated with at least a 2,500 mL infusion. An antiemetic agent could be administered at the discretion of each patient’s physician. The treatment regimen was repeated every 5 weeks at least two cycles unless disease progression or unacceptable toxicity occurred. A leukocyte count of ≥3,000/μL and the entry eligibility criteria regarding organ functions had to be satisfied to start the next cycle. If these criteria were satisfied 4 weeks after day 1 of each cycle of chemotherapy, the next cycle could be administered. The doses of S-1 were adjusted according to the degree of hematologic and nonhematologic toxicity. The dose was reduced by one level (20 mg per day) in patients whose BSA was ≥1.25 mg, with evidence of grade 4 hematologic toxicity or grade 3 or more nonhematologic 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 patient with BSA <1.25 m² experienced the above toxicities, then no further treatment with S-1 was done. If a rest period of >4 weeks was required, then the patient was withdrawn from the study.

Evaluation of Response and Toxicity. All eligible patients who received any part of the treatment were considered assessable for response and toxicity. Chest X-ray, complete blood count, and blood chemistry studies were repeated weekly. The response was assessed based on the chest X-ray or computed tomography scan findings that initially had been used to define the tumor extent. The response was evaluated in accordance with the criteria of the World Health Organization (12). A central radiological review was done to determine the eligibility of patients and the response of treatment. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical Analysis. The number of patients to be enrolled in this study was calculated to be 54, which was required to reject the null hypothesis that the lower bound of 95% CI of the expected response rate (50%) would be <30% under the conditions of α error of 0.025 (one side) and β error of 0.2. The overall survival of the eligible patients was defined as the time from the start of the treatment until death from any cause, and it was estimated by the Kaplan-Meier method. Differences between the proportions were evaluated by the χ² test. The data were considered to be significant when the P value was ≤0.05.

RESULTS

Patient Population. Between September 2000 and November 2001, 56 patients were enrolled in this study. One patient was considered to be ineligible because of prior treatment for pleurodesis in which OK432 was used for his malignant pleural effusion. The clinical characteristics of all eligible 55 patients are listed in Table 1. They included 41 men and 14 women, with a median age of 64 years. Thirty (55%) patients were treated with cisplatin at mid-cycle of administration of UFT for advanced non–small-cell lung cancer.
had Eastern Cooperative Oncology Group performance status of 0 and 45 (82%) patients had stage IV disease. The predominant histology type was adenocarcinoma (67%).

**Response and Survival.** Among all 55 eligible patients, 1 had a complete response and 25 had a partial response. Thus, the overall response rate was 47% (95% CI, 34–61%). Because one ineligible patient had a partial response, the overall response of all registered 56 patients was 48% (95% CI, 35–62%). The responding patients were classified in terms of the items shown in Table 2. There was no statistically significant difference in the response rates between the items compared. The median response duration was 4.2 months.

The median follow-up period was 28 months (range, 20–33 months). As shown in Fig. 1, median survival time of the 55 eligible patients was 11 months and the 1-year and 2-year survival rates were 45% (95% CI, 32–59%) and 17% (95% CI, 6–27%), respectively.

**Adverse Events.** The adverse events observed throughout the treatment of the 55 eligible patients are shown in Table 3. Among the hematologic adverse event, grade 3/4 neutropenia and anemia was observed in 29 and 22% of the patients, respectively. However, grade 3 thrombocytopenia was observed in only one patient (2%), and no patient had grade 4 thrombocytopenia. Among the observed nonhematologic adverse events, no grade 4 level was observed. There were no unexpected toxicities.

**Compliance.** A range of 1 to 12 treatment cycles were administered (1 cycle, 6 patients; 2 cycles, 18 patients; 3 cycles, 5 patients; 4 cycles, 12 patients; >4 cycles, 14 patients). The reasons for only one cycle of treatment were progressive disease in 4 patients and adverse events in 2 patients. The dose of S-1 was reduced in 8 patients because of adverse events including myelosuppression in 4 patients, gastrointestinal toxicity in 2 patients, glycemia in 1 patient, and dermatitis in 1 patient. A total of 197 cycles were given to the 55 patients. Sixty-nine (49%) of 142 treatment cycles excluding the first cycle was given at 4-week interval, 58 (40%) were at a 5-week interval, and 15 (11%) were at a >5-week interval.

**DISCUSSION**

Because the half-life of 5-FU is as short as 5 to 20 minutes (13) and the antitumor activity of 5-FU is time dependent, the continuous intravenous administration of 5-FU is considered to be appropriate rather than a bolus intravenous injection of 5-FU. In fact, a meta-analysis of six randomized trials in patients with colorectal cancer showed that the response rate was clearly higher for continuous infusion of 5-FU over 5 consecutive days than for weekly bolus injection of 5-FU (14). Although NSCLC has also been reported not to respond to a bolus injection of 5-FU (15), whether or not continuous treatment with 5-FU is effective for NSCLC remains unclear. However, studies have shown that a combination of cisplatin and protracted intravenous injection of 5-FU is effective for NSCLC (16). In prior trials, we used this combination chemotherapy with daily oral administration of UFT in place of the protracted intravenous injection of 5-FU which negatively affects the quality of life of a patient for advanced NSCLC (9–11).

The combination chemotherapy of cisplatin and 5-FU has been proven to have synergic antitumor effect in many experimental and clinical studies (17, 18). However, the optimal sequence for the administration of these drugs has yet to be determined. The sequence of cisplatin followed by 5-FU has been shown to be more cytotoxic than the reverse succession in in vitro and in vivo studies (19, 20) whereas the sequence of 5-FU followed by cisplatin has been proven to have a greater

**Table 2** Patient characteristics in relation to the response

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
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<td>1</td>
<td>25</td>
<td>23</td>
<td>6</td>
<td>47</td>
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<td>15</td>
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<td>18</td>
<td>5</td>
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<td>49</td>
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<td></td>
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<td></td>
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<tr>
<td>Adenocarcinoma</td>
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<td>0</td>
<td>15</td>
<td>17</td>
<td>5</td>
<td>41</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>14</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>57</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>75</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

**Table 3** Hematologic and nonhematologic toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade</th>
<th>Frequency of 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>13</td>
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<td>Anemia</td>
<td>14</td>
<td>24</td>
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<tr>
<td>Thrombocytopenia</td>
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<td>4</td>
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<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
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<td>1</td>
</tr>
<tr>
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<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
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<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>3</td>
</tr>
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<td>2</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>13</td>
<td>0</td>
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</table>

Fig. 1 Overall survival. Each tick represents a patient who is alive. The bars represent the 95% confidence interval of the survival rate at 1 year and 2 years after treatment.
antitumor activity than the opposite order of administration in tumor-bearing animals (21). Therefore, in our prior trials using UFT, we designed a treatment regimen that is thought to be a compromise solution between the present conflicting experimental data; namely, a daily administration of UFT from day 1 to 14 or 21 and a bolus infusion of cisplatin on day 8 (9, 10).

In the present study with S-1, the treatment modality was determined based on the UFT trials (9, 10) and phase II trial of S-1 combined with cisplatin in patients with advanced gastric cancer (22). The dose of cisplatin was decreased from 80 mg/m² in prior UFT trial to 60 mg/m² in the present trial because phase I trial indicated that 60 mg/m² of cisplatin on day 8 was the recommended dose when it was combined with daily administration of S-1 from day 1 for 3 weeks (22). Concerning the dose of cisplatin in combination chemotherapy in NSCLC patients, the effect of the dosage on survival has not yet been clearly elucidated. Klastersky et al. (23) reported the median survival time of patients who received vindesine plus combination chemotherapy consisting of either 60 or 120 mg/m² of cisplatin to be 7.6 and 6.4 months, respectively, and no overall survival difference between the two groups was observed (P = 0.138). On the other hand, the incidence of adverse events was significantly higher in the 120-mg dose than that in 60-mg dose.

Although a comparison between the present S-1 trial and the prior UFT trial with 108 patients (10) has limitation because of different trials, the response rate and survival seems to be favorable in the present trial despite the fact that proportion of stage IV patients in the present trial was higher than that in the UFT trials (82% versus 68%). The response rate and median survival time was 47% and 11.2 months in the present study and 29% and 10 months in the UFT trial, respectively. The frequency of severe adverse events in the both trials was similarly low.

The standard chemotherapy regimen for NSCLC is considered to be a platinum-based two-drug combination chemotherapy that uses paclitaxel, docetaxel, gemcitabine, or vinorelbine. The response rate and median survival time in the recent phase III trials that use these combination chemotherapies have been reported to be 17 to 28% and 7 to 9 months, respectively. Grade 3 or 4 hematologic and nonhematologic adverse events were observed in 57 to 76% (neutropenia) and 4 to 35% (vomiting), respectively (24, 25). In the present study with S-1 and cisplatin, the incidence of those adverse events seems to be lower than the above mentioned data. In addition, the antitumor mechanism is different from those agents. On the basis of these observations, we plan to conduct a randomized trial comparing the present combination chemotherapy with standard platinum-based two-drug combination chemotherapy regarding survival and the quality of life.

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