A feasibility study of postoperative adjuvant chemotherapy with fluoropyrimidine S-1 in patients with stage II-IIIA non-small cell lung cancer

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1. INTRODUCTION

Lung cancer is the most common cause of cancer death worldwide (1). As advanced lung cancer is difficult to cure with surgery alone, even after complete resection, postoperative adjuvant treatments are recommended. It has been reported that patients with completely resected stage I, II, and IIIA non-small cell lung cancer (NSCLC) may benefit from postoperative cisplatin (CDPP)-based chemotherapy (2-5). Although CDPP-based chemotherapy is considered the standard regimen, severe toxicities are occasionally observed and chemotherapy-related death has been one of the problems with adjuvant treatments. As an alternative adjuvant treatment with fewer adverse reactions, oral adjuvant chemotherapy with uracil-tegafur (UFT) has been evaluated. UFT improved the overall survival in patients with completely resected early stage NSCLC (6, 7). Adjuvant chemotherapy with uracil-tegafur (UFT) improved survival among patients with completely resected stage I lung adenocarcinoma. S-1, an oral dihydropyrimidine dehydrogenase (DPD)-inhibitory 5-fluorouracil, is a more potent DPD inhibitor than UFT; therefore, we hypothesized that postoperative adjuvant chemotherapy with S-1 would be effective for advanced non-small cell lung cancer (NSCLC). We conducted a feasibility study of S-1 as postoperative adjuvant chemotherapy in patients with curatively resected pathological stage II and IIIA NSCLC. Methods: Adjuvant chemotherapy consisted of 9 courses (4-week administration, 2-week withdrawal) of S-1 at 80-120 mg/body per day. Twenty-four patients with completely resected NSCLC were enrolled in this study from November 2007 through December 2010. The primary endpoint was the rate of completion of the scheduled adjuvant chemotherapy. The secondary endpoints were safety, overall survival, and relapse-free survival. Results: Five patients were censored because of disease recurrence. The planned 9 courses of S-1 were administered to completion in 8 patients. Twelve patients completed more than 70% of the planned courses. Grade 3 adverse reactions, such as elevated total bilirubin (4.2%) and pneumonitis (4.2%), were observed, but there were no Grade 4 adverse reactions. Patients who completed more than 70% of the 9 courses demonstrated better overall survival than those who completed less than 70%. Conclusion: Postoperative administration of S-1 may be possible with few severe adverse events as adjuvant chemotherapy for patients with curatively resected pathological stage II-III A NSCLC. J. Med. Invest. 65: 90-95, February, 2018

Keywords: Non-small cell lung cancer, S-1, adjuvant chemotherapy, feasibility study.

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therapy in patients with completely resected NSCLC. The primary endpoint was the rate of completing the scheduled adjuvant chemotherapy. The secondary endpoints were safety, overall survival and relapse-free survival. We could not calculate the number of patients to be enrolled in this study based on statistical analysis because this study was an exploratory trial. Twenty-four patients with completely resected NSCLC were enrolled in this study from November 2007 through December 2010. The present study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board at each institution.

2.2. Patient eligibility

Patient eligibility required compliance with the following criteria: (1) histologically proven NSCLC, (2) pathological stage II-IIIA (according to the Union for International Cancer Control 6th edition) after complete resection, (3) no previous treatment except for surgery, (4) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, (5) age ≥ 20 and < 80 years. Patients also had to have adequate organ function: 3,000 ≤ leukocytes ≤ 12,000/mm^3; neutrophil count ≤ 1,500/mm^3; thrombocytes ≥ 100,000/mm^3; hemoglobin ≥ 9.0 g/dL; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 upper limit of normal (ULN); total bilirubin ≤ 1.5 mg/dL, creatinine ≤ 1.5 mg/dL, creatinine clearance (CCR) estimated using Cockcroft-Gault’s formula ≥ 50 mL/min, and PaO2 ≥ 60 mmHg. Any patients with a history of drug hypersensitivity, serious surgical or nonsurgical complications, or active secondary cancer were excluded. In addition, pregnant or lactating women were excluded. Written informed consent was obtained from all patients.

2.3. Treatment schedule

Administration of S-1 was started within 2-6 weeks after surgery. The treatment comprised 9 courses (4-week administration, 2-week withdrawal) of S-1 (FT, gimeracil, oteracil potassium; Taiho Pharmaceutical) at 80-120 mg per day according to body surface area (BSA): BSA < 1.25 m^2, 80 mg per day; 1.25 m^2 ≤ BSA < 1.5 m^2, 100 mg per day; and 1.5 m^2 ≤ BSA, 120 mg per day. S-1 was administrated orally twice daily after meals for 4 weeks, and was thereafter withdrawn for 2 weeks. We checked drug compliance in an interview when patients visited the hospital. Administration of S-1 was temporarily discontinued if a patient had any of the following toxicities: leukocyte count < 2.0×10^3 cells/mL, neutrophil count < 1.0×10^3 cells/mL, platelet count < 75×10^3 cells/mL, total bilirubin > 1.5×ULN, ASTs > 150 IU/L, ALTs > 100 IU/L, serum creatinine > ULN, Ccr < 50 mL/min, or other non-hematological toxicities: Grade 2. On restarting administration of S-1, the dose was reduced from 120 mg to 100 mg per day, or from 100 mg to 80 mg per day. When treatment was restarted within 7 days, the restart was judged to represent the same course after temporary discontinuation of drug administration. When treatment could not be restarted within 7 days, the course was skipped and restarted as the next course. Treatment was discontinued when the patient exhibited disease recurrence, secondary cancer or adverse reactions that were uncontrollable using dose modification or temporary discontinuation of drug administration. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) version 3.0.

2.4. Statistical analysis

In the present study, P-values and confidence intervals (CI) were double-sided, and P < 0.05 was considered to indicate a significant difference. The Kaplan-Meier method was used to estimate the time-to-event functions of overall survival and relapse-free survival. The log-rank test was used to test for possible differences between estimated time-to-event curves. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. Overall survival was defined as the time from the date of the start of treatment to the date of death or last contact. Relapse-free survival was as the time from the date of the start of treatment to the date of disease progression or death (whichever occurred first) or the date of last contact.

3. RESULTS

3.1 Patient characteristics

Table 1 shows the characteristics of the 24 patients enrolled in the present study. The average age of the patients was 70 years (range, 49-79 years). Thirteen patients were 70 years old or older. Lobectomy or pneumonectomy were performed on all patients.

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16</td>
<td>66.7%</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>33.3%</td>
</tr>
<tr>
<td>Age (years old)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>3</td>
<td>12.5%</td>
</tr>
<tr>
<td>60-69</td>
<td>8</td>
<td>33.3%</td>
</tr>
<tr>
<td>70-79</td>
<td>13</td>
<td>54.2%</td>
</tr>
<tr>
<td>Type of resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>21</td>
<td>87.5%</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>3</td>
<td>12.5%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>19</td>
<td>79.2%</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4</td>
<td>16.7%</td>
</tr>
<tr>
<td>Adenosquamous cell carcinoma</td>
<td>1</td>
<td>4.2</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>8</td>
<td>33.3%</td>
</tr>
<tr>
<td>IIB</td>
<td>6</td>
<td>25.0%</td>
</tr>
<tr>
<td>IIIA</td>
<td>10</td>
<td>41.7%</td>
</tr>
</tbody>
</table>

3.2 Drug compliance

Table 2 shows drug compliance in each course and reasons for the discontinuation of drug administration. The planned 9 courses of S-1 were administrated to completion in 8 patients. Five patients were censored because of disease recurrence, and therefore the completion rate was calculated to be 42.1%; the average number of accomplished courses was 6.3. Twelve patients completed more than 70% of the planned courses. Among these 12 patients, 5 required dose reduction (41.7% of 12 patients). Ten patients discontinued drug administration because of adverse reactions. One patient refused to continue drug administration because of financial problems.

3.3 Adverse events

Table 3 shows a summary of the adverse reactions. Among the adverse reactions, Grade 1 or 2 anorexia (58.3%) was the most frequent, followed by diarrhea (29.2%), and fatigue (25.0%), which were reasons for the discontinuation of drug administration. Although Grade 3 total bilirubin elevation and pneumonitis were...
observed in one patient out of 24 patients (4.2%) each, no Grade 4 adverse reactions were noted. There were no treatment-related deaths.

3.4 Survival

Among the 24 patients followed for survival information, 10 had died and 14 were still alive at the time of analysis. The median follow-up time was 70 months (range, 9.5-97.9). At the time of analysis, the median overall survival was 92.4 months (95% CI, 45.5-139.3) (Figure 1). Fourteen patients relapsed, and the median relapse-free survival was 45.5 months (95% CI 16.1-75.0) at the time of analysis (Figure 2). Among 14 patients who relapsed, there were thorax recurrences in 11 patients. There were distant metastases in 3 patients, and metastases of multiple bones, supraclavicular lymph nodes, and adrenal glands were each observed in 1 patient. Except for patients who discontinued treatment because of disease recurrence, overall survival and relapse-free survival were not significantly different between patients who completed the planned 9 courses and those who did not; however, patients who completed more than 70% of the 9 courses exhibited better overall survival than those who completed less than 70% (log-rank test \( p = 0.038 \)). In the Cox proportional hazards regression model, completion of more than 70% of the courses was not statistically significant prognosticators for overall survival (Table 4). The relapse-free survival rate also tended to improve in patients who completed more than 70% of the planned courses \((p=0.066)\) (Figure 3).

### Table 2. Drug compliance (each course) (n=24)

<table>
<thead>
<tr>
<th>Course</th>
<th>Number of patients entering the course</th>
<th>Percentage</th>
<th>Reasons for discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24</td>
<td>100%</td>
<td>Grade 2 anorexia (patient refusal)</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>95.8%</td>
<td>Grade 2 anorexia (patient refusal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 2 fatigue (patient refusal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>79.2%</td>
<td>Grade 3 Pneumonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 2 anorexia and weight loss (patient refusal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>66.7%</td>
<td>Grade 1 fatigue (patient refusal)</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>62.5%</td>
<td>Financial problem (patient refusal)</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>62.5%</td>
<td>Grade 2 Vomiting (patient refusal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 2 Thrombocytopenia and elevated T-bil (patient refusal)</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>50.0%</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3 elevated T-bil</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>41.7%</td>
<td>Recurrence</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>33.3%</td>
<td>Grade 2 Weight loss and grade 1 anorexia (patient refusal)</td>
</tr>
</tbody>
</table>

### Table 3. Adverse reactions (n=24)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total (Incidence %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Laboratory Findings</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>6</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>4</td>
</tr>
<tr>
<td>Elevated T-bil</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Findings</td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Heartburn</td>
<td>2</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
</tr>
</tbody>
</table>

**Clinical Findings**

- Pigmentation | 8   | 1   | 0   | 0   | 37.5 |
- Dry dermatitis | 1   | 0   | 0   | 0   | 4.2 |
- Itch sensation | 1   | 0   | 0   | 0   | 4.2 |
- Sense of fatigue | 5   | 1   | 0   | 0   | 25.0 |
- Pneumonitis | 0   | 0   | 1   | 0   | 4.2 |
- Weight loss | 1   | 2   | 0   | 0   | 12.5 |
- Dacryorrhea | 2   | 0   | 0   | 0   | 8.3 |
- Vertigo | 1   | 0   | 0   | 0   | 4.2 |
- Nosebleed | 1   | 0   | 0   | 0   | 4.2 |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

![Figure 1. Overall survival of the 24 patients. The median overall survival was 92.4 months (95% CI, 45.5-139.3).](image)

### 4. DISCUSSION

The present study was carried out to confirm the feasibility of adjuvant chemotherapy with S-1 in patients with curatively resected pathological stage II and IIIA NSCLC. The completion...
rate of the scheduled 9 courses of S-1 administration was 42.1%. The completion rate of more than 70% of the scheduled 9 courses was 63.2%. No Grade 4 adverse reactions were observed throughout the 9 courses. Only 2 Grade 3 adverse reactions were encountered (8.3% of total). There were no significant differences in the overall survival rate or the relapse-free survival rate between the treatment completion group and the incompletion group; however, the overall survival rate was improved in patients who completed more than 70% of the scheduled 9 courses.

Adjuvant chemotherapy after curative surgery with the single-agent S-1 has been proven to improve the overall survival rate in patients with gastric cancer in a randomized phase III trial (11). In that study, adjuvant chemotherapy consisted of 8 cycles (4 weeks of administration and 2 weeks of withdrawal) of S-1 at the same daily dose as that used in the present study (80-120 mg/body) and the completion rate was 65.8%, which was higher than that of the scheduled 9 courses in the present study. In the previous study, the mean age of the patients was 60.3 years and only approximately 30% of the patients were older than 70 years. In the present study, the mean age was 68.1 years and approximately 50% of the patients were older than 70 years. Considering this age difference among the patients in the different studies, the completion rate of the present

![Figure 2](image1.png)

**Figure 2.** Relapse-free survival among 24 patients. The median relapse-free survival was 45.5 months (95% CI 16.1-75.0).

Table 4. Cox proportional hazard regression analysis for overall survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp(B)</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Sex Male versus Female</td>
<td>1.684</td>
<td>0.196-14.437</td>
</tr>
<tr>
<td>Age (years) ≥70 versus &lt; 70</td>
<td>8.325</td>
<td>0.937-73.987</td>
</tr>
<tr>
<td>Histology Adenocarcinoma versus others</td>
<td>1.526</td>
<td>0.178-13.086</td>
</tr>
<tr>
<td>pStage II versus III</td>
<td>3.223</td>
<td>0.589-17.640</td>
</tr>
<tr>
<td>Completion rate (%) ≥70 versus &lt; 70</td>
<td>0.140</td>
<td>0.016-1.212</td>
</tr>
</tbody>
</table>

![Figure 3](image2.png)

**Figure 3.** Overall survival (OS) (A) and relapse-free-survival (RFS) rates (B). Except for the patients who discontinued treatment because of disease recurrence, in the over 70% of completed courses group, OS was improved and the RFS rate also tended to improve compared with the under 70% completed courses group.
There were few severe adverse events in the present study. Currently, the standard regimen for adjuvant chemotherapy in postoperative patients with stage II-IIIA NSCLC is cisplatin doublet. The LACE Collaborative Group published a meta-analysis of the 5 largest randomized cisplatin-based trials (5). The LACE meta-analysis demonstrated that both overall survival and disease-free survival were improved with the administration of cisplatin. However, there was a significant interaction between chemotherapy effects and World Health Organization (WHO) performance status (PS). In the 5 trials, the rate of overall Grade 3 to 4 toxicity was 66%. It is difficult for patients with a poor PS to receive cisplatin-based chemotherapy because of this high level of toxicity. In the present study, the rate of Grade 3 toxicity was 8.3% and there were no Grade 4 toxicities. Adjuvant chemotherapy with S-1 was performed with few severe adverse events. The most common adverse events were Grade 1 or 2 anorexia (54.2%), which was the reason for discontinuation of S-1 administration. Gastrointestinal toxicities, such as oral mucositis and diarrhea, were also frequent; thus, the completion rate may improve with supportive therapies for gastrointestinal toxicity and with a frequent withdrawal schedule of S-1.

There was a significant benefit for the overall survival rate in patients who completed more than 70% of the scheduled 9 courses. Although there were no significant differences, the relapse-free survival rate tended to improve in patients who completed more than 70% of the scheduled 9 courses. In the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) (11), a randomized phase II study of chemotherapy with S-1 after curative surgery in Japanese patients with locally advanced gastric cancer, the overall survival rate and the relapse-free survival rate in the S-1 group at 5 years were better than in the surgery-only group. In the same study, patients who completed more than 70% of the planned courses exhibited better overall survival than those who completed less than 70%. The same trend was seen in our present study. Based on ACTS-GC data, adjuvant chemotherapy with S-1 after curative resection of advanced gastric cancer is considered the standard regimen. In NSCLC, some feasibility studies of postoperative chemotherapy with S-1 have been performed as an ambulatory treatment. Patients were truthful about drug compliance because S-1 therapy was performed with few severe adverse events as adjuvant chemotherapy for advanced lung cancer.

There are some limitations in this study. First, the number of patients in this study is not enough to draw definitive conclusions from the prognostic analysis. Second, we checked drug compliance in an interview, and had no way of verifying whether the patients were truthful about drug compliance because S-1 therapy was performed as an ambulatory treatment. In conclusion, postoperative administration of S-1 may be possible with few severe adverse events as adjuvant chemotherapy for patients with curatively resected pathological stage II-III A NSCLC. S-1 can be administered orally with few toxicities; therefore, it is expected to be a promising agent for adjuvant chemotherapy in advanced lung cancer. Based on this feasibility study, a randomized trial to evaluate the efficacy of S-1 as adjuvant chemotherapy with low toxicity for resected advanced NSCLC is required in the future.

**CONFLICT OF INTEREST**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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**Table 5. Selected phase II clinical trials of adjuvant chemotherapy with S-1 for completely resected NSCLC.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Dose/ schedule</th>
<th>Planned courses</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Per day</td>
<td>On days</td>
<td>Duration</td>
</tr>
<tr>
<td>Yano (2010)</td>
<td>S-1</td>
<td>80-120 mg</td>
<td>1-14</td>
<td>q4wks</td>
</tr>
<tr>
<td>Tsuchiya (2012)</td>
<td>S-1</td>
<td>80-120 mg</td>
<td>1-28</td>
<td>q6wks</td>
</tr>
<tr>
<td>Niho (2013)</td>
<td>DOC+CDDP</td>
<td>60 mg/m²</td>
<td>Day 1</td>
<td>q3-4wks</td>
</tr>
<tr>
<td></td>
<td>followed by S-1</td>
<td>80 mg/m²</td>
<td>Day 1</td>
<td>q3-4wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg/m²</td>
<td>1-14</td>
<td>q3wks</td>
</tr>
<tr>
<td>Okumura (2013)</td>
<td>S-1</td>
<td>80 mg/m²</td>
<td>1-28</td>
<td>q6wks</td>
</tr>
<tr>
<td>Maruyama (2014)</td>
<td>S-1</td>
<td>50-100 mg</td>
<td>1-14</td>
<td>q3wks</td>
</tr>
</tbody>
</table>
REFERENCES