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CLINICAL INVESTIGATION **Lung**

PHASE I STUDY OF ORAL S-1 PLUS CISPLATIN WITH CONCURRENT RADIOTHERAPY FOR LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER

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Purpose: To determine the maximum tolerated dose (MTD) and recommended dose (RD) of S-1 in combination with cisplatin and thoracic radiotherapy in patients with unresectable Stage III non–small-cell lung cancer (NSCLC).

Methods and Materials: S-1 was administered orally twice daily for 14 days and cisplatin on Days 1 and 8 of each cycle; this was repeated every 3 weeks. Doses of each drug were planned as follows: level 0, 50/40; level 1, 60/40; level 2, 70/40; level 3, 80/40 (S-1 [mg/m^{-2}/day^{-1}]/cisplatin [mg/m^{-2}/day^{-1}]). Thoracic radiation therapy was administered in 2 Gy fractions five times weekly to a total dose of 60 Gy.

Results: Ten patients were enrolled in this study. All patients received 60 Gy of thoracic radiotherapy and 7 (70%) patients received four cycles of chemotherapy. At level 1, 2 of 3 patients experienced a delay exceeding 10 days in the cisplatin administration of Day 29. Grade 4 neutropenia and Grade 3 fever occurred in 1 and 1 patients, respectively. Nonhematologic toxicities were mild. None developed ≥Grade 3 esophagitis or lung toxicity. At level 0, 2 of 7 patients developed dose-limiting toxicity. Thus, level 1 was considered the MTD and Level 0 was selected as the RD. Objective responses were seen in all patients.

Conclusions: The RD is the level 0 dose, and this regimen is a feasible and well-tolerated regimen for the treatment of patients with Stage III NSCLC. © 2009 Elsevier Inc.

S-1, Cisplatin, Phase I study, Non–small-cell lung cancer, Chemoradiotherapy, Concurrent.

INTRODUCTION

Stage III locally advanced non–small-cell lung cancer (NSCLC) accounts for about 25% of all lung cancer cases (1). Combined chemoradiotherapy is the standard treatment for NSCLC with unresectable Stage III disease and a good performance status (1, 2). Recent randomized Phase III trials have shown that concurrent chemoradiotherapy is superior to chemotherapy followed by radiotherapy in terms of the response and survival in such patients (3, 4). However, concurrent chemoradiotherapy is also associated with an increased rate of bone marrow suppression and acute esophagitis compared with sequential chemoradiotherapy.

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an oral anticancer agent comprising tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate, in a molar ratio of 1:0.4:1 (5). Tegafur, a prodrug of 5-fluorouracil (5-FU), is gradually converted to 5-FU and is rapidly catabolized by dihydropyrimidine dehydrogenase in the liver. 5-chloro-2, 4-dihydroxypyridine is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting dihydropyrimidine dehydrogenase (6). When combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations, both in plasma and in tumor. In addition, it has been suggested that 4-dihydroxypyridine has the potential to enhance the antitumor activity of 5-FU against subcutaneous tumor in nude mice (7). Potassium oxonate is an agent that decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme pyrimidine phosphoribosyl transferase. Potassium oxonate preferentially localizes in

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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 (8).

In a Phase II study of S-1, which was orally administered at approximately 40 mg/m^{-2} twice per 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 4 toxicity was low (9). 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 (10).

Both cisplatin and 5-FU have been reported to have a radiosensitizing effect in preclinical and clinical studies including NSCLC (11–13). Clinically, uracil/tegafur plus cisplatin with concurrent radiotherapy is described to be a feasible and effective treatment for locally advanced NSCLC (14). Furthermore, a recent preclinical study has shown that gimeracil, a dihydropyrimidine dehydrogenase inhibitor combined in S-1, has a potent radiosensitizing property (15). Preclinical studies using human oral cancer xenograft models has demonstrated that the combination of S-1 and fractionated radiotherapy is more effective than either agent alone (16). Several researchers described that oral S-1 and concurrent radiotherapy is well tolerated and feasible in pancreatic cancer and rectal cancer (17, 18). In *in vivo* study, the enhanced effects on the inhibition of tumor growth were observed when cisplatin was combined with radiotherapy (11).

Against this background, we conducted a Phase I study of oral S-1 plus cisplatin with concurrent radiotherapy for locally advanced NSCLC to determine the maximum tolerated dose (MTD) to be investigated further in a Phase II study.

METHODS AND MATERIALS

Patient eligibility

Eligible patients were required to have: histologically or cytologically proven unresectable Stage IIIA or IIIB NSCLC; no previous chemotherapy or radiotherapy; a performance status of 0-1 on the Eastern Cooperative Oncology Group scale; an age between 20 years and 74 years; a life expectancy of 12 weeks or more; adequate bone marrow reserve (leukocyte count $\geq$4,000 mm^{-3}, neutrophil count $\geq$2,000 mm^{-3}, platelet count $\geq$100,000 mm^{-3}, and hemoglobin $\geq$10 g/dL^{-1}); normal liver function (total serum bilirubin $\leq$1.5 mg/dL^{-1}, and aspartate transaminase and alanine transaminase less than twice the upper limit of the normal range), normal renal function (normal serum creatinine and blood urea nitrogen levels), and pulmonary function (PaO_2 $\geq$70 torr). Patients were excluded if they had malignant pleural or pericardial effusion; active double cancer; a concomitant serious illness, such as uncontrolled angina pectoris; myocardial infarction in the previous 3 months; heart failure; uncontrolled diabetes mellitus; uncontrolled hypertension; interstitial pneumonia or lung disease; infection or other diseases contraindicating chemotherapy or radiotherapy; pregnancy; or breastfeeding. The local ethics committee approved the study and written informed consent was obtained from all patients.

Clinical study design

This was an open-label, single-center, single-arm, dose-escalating Phase I study. S-1 was administered orally twice daily after a meal for 14 consecutive days, followed by a 1-week break. Each capsule of S-1 contained 20 or 25 mg of tegafur. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. Cisplatin was administered on Days 1 and 8 by intravenous infusion over 60 minutes together with 2,500–3,000 mL fluid hydration. All patients received prophylactic antiemetic therapy consisting of a 5HT3-antagonist and a steroid. This chemotherapy regimen was repeated every 3 weeks for four cycles. The dose of each drug in this study was planned as follows: level 0, S-1 50 mg/m^{-2}/day^{-1} and cisplatin 40 mg/m^{-2}; level 1, S-1 60/mg m^{-2}/day^{-1} and cisplatin 40 mg/m^{-2}; level 2, S-1 70 mg/m^{-2}/day^{-1} and cisplatin 40 mg/m^{-2}; and level 3 was S-1 80 mg/m^{-2}/day^{-1} and cisplatin 40 mg/m^{-2}.

Radiation therapy was administered using 10-MV X-rays in 2 Gy fractions five times weekly. All patients' treatment plans were designed on a commercial treatment planning system (XiO version 4.2.1, CMS, St. Louis, MO). The treatment planning was based on a 5-mm thickness, and 5-mm interval computed tomography (CT) scans obtained in the treatment position. CT images were obtained under normal quiet breathing through the all images and ''slow'' scan technique (3 s per rotation) was used around the primary tumor. The gross tumor volume was delineated according to the primary tumor and nodal involvement determined from CT and 18F-fluorodeoxyglucose positron emission tomography information. The clinical target volume was defined and contoured with 5-10 mm around the gross tumor volume and contours around regional lymph node regions, i.e., ipsilateral hilum and the mediastinum. Planning target volume–1 included the clinical target volume plus a 5- to 10-mm margin; planning target volume–2 included the gross tumor volume plus a 10-mm margin. An additional margin (typically 5 mm) was added if necessary. Beam shaping was performed using a multileaf collimator. The beam arrangements were anteroposterior parallel opposed fields followed by off-cord oblique fields in all patients. The standard of practice was to prescribe 60 Gy to planning target volume–2 and 40 Gy to planning target volume–1 with concurrent chemotherapy. Other objectives were to restrict the relative volume of normal lung treated to a dose above 20 Gy (V20) to be below 30% and the maximum spinal cord dose was restricted to be below 44 Gy. The dose was prescribed to the isocenter of this point. Tissue heterogeneity correction was performed and the superposition dose calculation algorithm was used. The normal lung volume was contoured automatically by CT threshold, the trachea and bronchi were excluded manually, and the gross tumor volume within the lung was excluded automatically. Moreover, esophageal dosimetric parameter was evaluated. The esophagus was defined from the inferior border of the cricoid cartilage to the gastroesophageal junction. The external surface of the esophagus was contoured on each axial slice of the CT images. The following dosimetric parameters were generated from the dose–volume histogram for total normal lung: the percent of the total lung volume exceeding 20 Gy, the total lung volume mean dose and for esophagus: the percent of the esophageal volume exceeding 45 Gy because this predicts the risk of radiation esophagitis (19).

The prophylactic administration of granulocyte-colony stimulating factor was not permitted. Administration of granulocyte-colony stimulating factor was permitted in patients with Grade 4 neutropenia or Grade 3 febrile neutropenia. Subsequent courses of chemotherapy were initiated when the leukocyte counts were 4,000 mm^{-3} or more and platelet counts were 100,000 mm^{-3} or more after