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Phase I/II trial of gemcitabine plus oral TS-1 in elderly patients with advanced non-small cell lung cancer: Thoracic oncology research group study 0502

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ABSTRACT

A phase I/II trial of TS-1 combined with gemcitabine was designed to determine the maximum tolerated dose (MTD) and recommended dose (RD) and to evaluate the efficacy and toxicity in elderly patients with advanced non-small cell lung cancer (NSCLC). Patients older than 70 years of age received TS-1 orally b.i.d. on days 1–14 and gemcitabine intravenously on days 8 and 15 every 4 weeks. In phase I ($n = 22$), each cohort received escalating doses of TS-1 (30–40 mg/m^2 b.i.d.) and gemcitabine (800–1000 mg/m^2); MTD was 40 mg/m^2 b.i.d. TS-1 and 1000 mg/m^2 gemcitabine; RD was 30 mg/m^2 b.i.d. TS-1 and 1000 mg/m^2 gemcitabine. Dose-limiting toxicities included a grade 3 infection, skin toxicity, and stomatitis. In phase II ($n = 37$), the overall response rate was 27% (90% confidence interval (CI): 15–42%) and the median time to progression and overall survival were 4.2 months (90% CI: 3.2–5.7) and 12.9 months (90% CI: 10.4–14.7), respectively. The most common grade 3 or higher toxicity was neutropenia (45.9%), and thrombocytopenia was observed in 13.5% of patients. Two cases each of grade 3 pneumonitis and skin toxicity were observed, but nonhematological toxicities occurred at generally low frequencies. TS-1 with gemcitabine is a promising doublet regimen in elderly patients with advanced NSCLC with acceptable toxicities.

1. Introduction

Non-small cell lung cancer (NSCLC) is a leading cause of cancer death. Most patients with NSCLC have metastatic disease or malignant pleural effusion at the time of diagnosis and require systemic treatment. The number of elderly patients with NSCLC is increasing yearly [1] and the current standard treatment for those patients is single-agent chemotherapy with either vinorelbine, gemcitabine, or docetaxel [2–4]. The choice of these treatments is based largely on the results of a randomized phase III study from Italy comparing vinorelbine or gemcitabine monotherapy to a combination of vinorelbine plus gemcitabine for patients 70 years or older [3]. Although this study failed to show survival benefit for combination chemotherapy over monotherapy, the 1-year survival rate with these single-agents remains 30–40% at most. Therefore, the development of effective combination chemotherapy with a low incidence of toxicity is strongly warranted.

Tegafur-uracil (UFT) is an oral agent composed of a 1:4 molar ratio of tegafur, a prodrug that is converted to fluorouracil (5-FU), and uracil, which elevates serum levels of 5-FU by inhibiting its enzymatic degradation [5]. Previous studies have extensively suggested a potential synergistic effect between 5-FU and gemcitabine [6–8] in both *in vitro* and clinical studies. We conducted phase I and II studies of combination chemotherapy with daily administration of UFT for 2 weeks and a bolus injection of gemcitabine on days 8 and 15 as a first-line treatment for advanced NSCLC [9,10]. The phase II study in 44 patients demonstrated a promising objective response rate (ORR) of 41% and a median survival time of 13.2

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months with an incidence of grade 3 or higher nonhematological adverse events of less than 5% and tolerable myelosuppression. The regimen also showed a high antitumor activity in a subset of 21 patients 75 years or older (ORR = 38%) [9].

TS-1 (Taiho Pharmaceutical Co., Tokyo, Japan) is a new oral anticancer agent that is composed of tegafur, 5-chloro-2, 4-dihydroxypyridine (CDHP), and potassium oxonate in a molar ratio of 1:0.4:1. The 5-FU concentrations in blood and tumors achieved by TS-1 are much higher and longer-lasting than those by UFT [11]. In a phase II trial of TS-1 monotherapy in previously untreated patients with advanced NSCLC, the ORR was 22% and the median survival time was 10.2 months [12]. A phase I/II trial of TS-1 plus gemcitabine was conducted to further enhance the efficacy of the combination of UFT plus gemcitabine, while maintaining a mild level of toxicity in the treatment of elderly patients.

2. Patients and methods

2.1. Patient eligibility

Patients were registered at the central data center when the following eligibility criteria were confirmed: cytologically or histologically confirmed NSCLC; stage IIIB disease without any indications for radiotherapy or stage IV disease; no prior treatment; age 70 years of age or older; and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The criteria for organ function included: neutrophil count $\geq$2000/μL; platelet count $\geq$100,000/μL; hemoglobin level $\geq$9.5 g/dL; serum bilirubin concentration $\leq$1.5 mg/dL; serum aspartate aminotransferase and alanine aminotransferase concentrations $\leq$100 IU/L; creatinine level $\leq$1.3 mg/dL; creatinine clearance rate $\geq$30 mL/min ($\geq$60 mL/min for the phase II portion); and arterial oxygen saturation $\geq$90%.

Patients were excluded from the study if they had either interstitial pneumonia or pulmonary fibrosis on chest X-ray films, any severe concomitant disease (severe cardiac disease, uncontrolled diabetes mellitus, severe infection), concomitant malignancy, pleural effusion necessitating treatment, or symptomatic cerebral involvement. Written informed consent was required from all patients. The protocol was approved by the institutional review committee of each of the participating institutions.

2.2. Evaluation for enrollment

All patients were required to undergo a computed tomography (CT) scan of the thorax and the upper abdomen, either CT or magnetic resonance imaging (MRI) of the brain and a radioisotopic bone scan for stage assessment. A complete blood cell count and a blood chemistry panel were also obtained at enrollment. After protocol treatment was started, the blood examinations and chest radiography were performed at least once per week. CT or MRI examinations were repeated every 6 weeks to evaluate the target lesions. The tumor response was assessed with the Response Evaluation Criteria in Solid Tumors, and toxicity was assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

2.3. Phase I portion

The primary endpoint for the phase I trial was to determine the maximum tolerable dose (MTD) and dose-limiting toxicity (DLT). The doses were escalated in each successive cohort of 3 or more new patients. TS-1 was administered orally twice daily after meals on days 1–4. Gemcitabine was administered intravenously in 30 min or less on days 8 and 15. The schedule was repeated every 4 weeks for more than 3 cycles, unless disease progression or unacceptable toxicity occurred. Satisfaction of the entry eligibility criteria regarding the organ function was required before the next cycle could be started.

Three dose levels were evaluated with the following doses: level 1, 30 mg/m^2 (60 mg/m^2/day) of TS-1 and 800 mg/m^2 of gemcitabine; level 2, 30 mg/m^2 of TS-1 and 1000 mg/m^2 of gemcitabine; and level 3, 40 mg/m^2 (80 mg/m^2/day) of TS-1 and 1000 mg/m^2 of gemcitabine. Gemcitabine was administered when the leukocyte count was $\geq$2000/μL, the thrombocyte count was $\geq$75,000/μL, and nonhematological toxicities were no greater than grade 1.

The dose level was escalated on the basis of the toxicity during the first cycle of chemotherapy and was not escalated for each individual. A DLT was defined as any of the following: (i) grade 4 neutropenia; (ii) grade 3 febrile neutropenia; (iii) grade 4 thrombocytopenia; (iv) grade 3 nonhematological adverse events (except anorexia and fatigue); (v) a delay of gemcitabine infusion on day 15 for more than 7 days; and (vi) a delay of administration of the next course for more than 2 weeks. If DLT occurred in 1 or 2 of the 3 initial patients at a particular dose level, then 3 additional patients were treated at the same dose level. If DLT developed in all 3 patients or in 3 of 6 patients, then enrollment was stopped at this dose level, which was defined as the MTD. The preceding dose level was designated as the recommended dose (RD) for the phase II portion.

2.4. Phase II portion

The primary endpoint for the phase II study was the ORR. The patients were enrolled until the number of those treated with RD, including the patients who received the RD in the phase I portion, reached the predetermined sample size. The treatment schedule used in phase I was also followed in the phase II portion.

2.5. Statistical analysis

The phase II portion was designed to detect the difference between the ORRs of 0.10 and 0.30 with more than 90% power (exact binomial test for one sample proportion, 1-sided $\alpha = 0.05$). The new regimen was to be considered worthy of further investigation if >7 responses were observed in a 37-patient cohort treated at the RD. The Kaplan–Meier method was used to estimate the median values of time-to-event variables, such as overall survival (OS) and progression-free survival (PFS), and their confidence intervals (CIs) were calculated with the Brookmeyer and Crowley method [13]. All analyses were performed with the SAS software package, version 9.1 (SAS Institute, Cary, NC).

3. Results

Forty-nine patients were enrolled from May 2005 through December 2006. The phase I portion had 22 patients. Thirty-seven patients, including 10 patients from the phase I portion who were treated with the RD level, were enrolled in phase II. The median age of all patients in the study was 77 years (range, 70–85 years). Thirty-two (65%) patients had an ECOG PS of 1, 28 (57%) patients had adenocarcinoma, and 32 (65%) patients had stage IV disease (Table 1).

3.1. MTD and DLT in the phase I portion

The phase I portion included 22 patients. At level 1, 1 of 6 patients had a DLT (grade 3 infection). Then, the dose was escalated to level 2 where 6 patients were enrolled and treated. However, 3 of them were not evaluable with regard to the DLT of TS-1/gemcitabine combination; 1 patient experienced sudden death which was unrelated to TS-1 on day 2 of the first cycle, and 2