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Phase I/II study of docetaxel and S-1, an oral fluorinated pyrimidine, for untreated advanced non-small cell lung cancer

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ABSTRACT

The purpose of this phase I/II study is to evaluate a new combination chemotherapy consisting of docetaxel and S-1 as front-line therapy for patients with untreated advanced non-small cell lung cancer (NSCLC). The treatment included docetaxel on day 1 and oral S-1 at a fixed dose of 40 mg/m^2 administered twice daily on days 1–14 and repeated every 3 weeks. In phase I, docetaxel at escalating doses of 40 (level 0), 50 (level 1) and 60 mg/m^2 (level 2) was administered starting from level 1. Because only one patient among the 6-patient cohort at level 1 and no patient among the 3-patient cohort at level 2 experienced defined dose-limiting toxicity (DLT), level 2 was determined as the recommended dose. In phase II, 60 patients were treated at the recommended dose for median 3 cycles, and the overall response rate was 30% (95% confidence interval [CI], 18.9–43.2%), and the median overall and progression-free survival times were 15.2 (95% CI: 10.5–17.7) and 4.9 (95% CI: 3.5–5.6) months, respectively. The most frequent toxicities experienced were neutropenia, febrile neutropenia and appetite loss; all toxicities were however well manageable. The present regimen showed a potent activity with mild toxicity in untreated NSCLC.

1. Introduction

The standard first-line treatment for advanced non-small cell lung cancer (NSCLC) is platinum-based two-drug combination chemotherapy of four to six cycles [1–4]. Recent studies have suggested survival advantage with the inclusion of molecular-targeted agents such as bevacizumab [5] or cetuximab [6] in the standard cytotoxic combination chemotherapy; however, additional toxicity is also observed. Although a meta-analysis demonstrated that a chemotherapeutic regimen that included a platinum agent was superior to a non-platinum regimen with statistical significance in terms of survival [7], the survival advantage of the former over the latter is not remarkable. A subset analysis of the meta-analysis, however, failed to show a significant advantage of the platinum-based regimen over the non-platinum regimen when the latter consisted of relatively newly developed agents (i.e., 3rd-generation-based combination regimens) [7]. From these viewpoints, although the standard therapy for advanced NSCLC is platinum-based combination chemotherapy, non-platinum regimen would be a promising alternative for certain patient populations such as patients desiring less emetogenic regimen or those with tumor harboring high ERCC1 expression rendering resistance to platinum agents. In addition, a less toxic non-platinum regimen would also be clinically relevant when considering that future additional bevacizumab or cetuximab would result in more serious toxicity than the current standard platinum-based regimen. Therefore, the development of more potent or less toxic non-platinum regimens with similar potential to platinum regimens is eagerly awaited.

S-1 is a recently developed orally administrated agent consisting of 5-chloro-2, 4-dihydoroxypyrimidine (CDHP), potassium oxonate (Oxo) and tegafur (FT), a prodrug of 5-fluorouracil (5-FU) [8]. FT is converted to 5-FU by hepatic microsomal P450 followed by phosphorylated activation in various tissues as well as in tumors [9]. Oxo inhibits this phosphorylation step in the intestine to decrease intestinal toxicity [10], and CDHP inhibits 5-FU degradation to neurotoxic F-β-Alα, leading to diminished neurotoxicity [11]. Thus, the combination of these three compounds renders intra-capsular

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biological modulations to enhance cancer cell killing capability and to minimize toxicity. S-1 is active against gastric cancer when combined with cisplatin [12,13], irinotecan [14] or docetaxel [15]. Its potential against NSCLC was suggested by a phase II study [16]. Docetaxel, on the other hand, is one of the most powerful agents against NSCLC [3], and a series of preclinical experiments has suggested potential synergism between docetaxel and fluorinated pyrimidines. That is, the combination of docetaxel and S-1 showed significantly higher efficacy in making tumors shrink than their single use in gastric cancer xenograft animal models [17,18]. Although the precise mechanisms remain to be clarified, these may include the following. Docetaxel causes suppression of thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPD), and induction of orotate phosphoribosyl transferase (OPRT) in gastric cancer cell lines [19]. On the other hand, patients with colorectal cancer treated with 5-FU have a better prognosis when the tumor has a lower level of TS and DPD [20], or a higher ratio of OPRT to DPD [21] than patients with tumors under different conditions.

Thus, a phase I/II study was conducted to determine the maximal tolerable dose (MTD) and to evaluate the clinical relevance of S-1 combined with docetaxel for patients with untreated advanced NSCLC.

2. Patients and methods

2.1. Eligibility

Patients meeting all the following criteria were enrolled in this multicenter trial: (i) confirmed untreated NSCLC of clinical stage IIIB or IV that is inadequate for curative-intent thoracic radiotherapy, (ii) a performance status (PS) (Eastern Cooperative Oncology Group) of 0–2, (iii) age ranging from 20 to 75 years, (iv) adequate organ functions (neutrophils $\geq 2000/mm^3$, platelets $\geq 100{,}000/mm^3$, total bilirubin ≤ 1.5 g/dl, AST/ALT ≤ 2.5-fold of the normal value, creatinine $\leq$ the normal value, creatinine clearance ≥ 50 ml/min, and $PaO_2 \geq 70$ Torr), (v) measurable lesions using response evaluation criteria in solid tumours (RECIST), (vi) life expectancy exceeding 3 months, and (vii) written informed consent. Patients with any of the following conditions were ineligible: (i) fever suggesting infectious diseases, (ii) past treatment with flucytosine, (iii) interstitial lung disease, (iv) history of hypersensitivity to any component of S-1 or docetaxel, (v) edema, pleural or pericardial effusion requiring treatment, (vi) requirement for continuous or intermittent oxygen therapy, (vii) any serious complications (e.g., liver cirrhosis, uncontrolled diabetes mellitus, heart disease, and myocardial infarction within 6 months interval before enrollment), (viii) superior vena cava syndrome, (ix) pregnancy or feeding, (x) symptomatic brain metastasis, or (xi) other inadequate conditions.

2.2. Pretreatment evaluation

Baseline evaluation included history with a complete record of concomitant medical conditions, physical examinations, PS, complete blood counts, serum chemistries and electrolytes, urinalysis, chest radiogram, chest computed tomography (CT), abdominal CT, brain magnetic resonance imaging with contrast medium enhancement otherwise contraindicated, and bone scintigram. These examinations were to be performed within 1-month prior to enrollment.

2.3. Drug administration

Chemotherapy consisted of oral S-1 (fixed dose: 40 mg/m^2 given twice daily on days 1–14) and docetaxel (escalating dose: 40 mg/m^2 in level 0, 50 mg/m^2 in level 1 or 60 mg/m^2 in level 2 on day 1) with a 7-day rest period. This regimen was repeated every 3 weeks for at least two courses and until progression unless defined dose reduction or stopping criteria were encountered. The dose of S-1 (40 mg/m^2) was simplified according to body surface area (BSA) because of the limitation in the available capsule contents as follows: 40 mg b.i.d. when BSA was lower than 1.25 m^2; 50 mg b.i.d. when BSA ranged from 1.25 to 1.5 m^2; 60 mg b.i.d. when BSA was 1.5 m^2 or higher.

In phase I, the first six patients were enrolled in level 1. When less than three patients among six experience a defined dose-limiting toxicity (DLT), the next three to six patients should be enrolled in level 2, whereas they should be enrolled in level 0 when three or more patients among six experience DLT. In level 2, this level should be the recommended dose when no patient among three or less than three patients among six experience DLT, whereas level 1 should be the recommended dose when three patients out of the first cohort, or three or more patients among six experience DLT. A docetaxel dose higher than 60 mg/m^2 was not evaluated because it is not approved for NSCLC in Japan. In level 0, this level should be the recommended dose when no patient among three or less than three patients among six experience DLT, whereas the next phase II study should be cancelled when three patients out of the first cohort, or three or more patients among six experience DLT. DLT was defined as grade three or four non-hematological toxicities (excluding nausea/vomiting, appetite loss, fatigue and hypersensitivity), febrile neutropenia, grade 4 neutropenia for more than 3 days, grade 4 thrombocytopenia, low compliance of S-1 of less than 10 days out of 14 days on day 21, or failure to start the second course at no later than day 29. DLT was evaluated only in the first course according to the Common Toxicity Criteria of Adverse Events (CTCAE) version 3.

In phase II, docetaxel at the recommended dose determined in the previous phase I study and S-1 were administered similarly to the phase I study in 60 patients including those in the phase I study who were eventually treated at the determined recommended dose. Post-treatment was withheld until evident disease progression, followed by no restriction afterward.

2.4. Evaluation during chemotherapy

Symptoms, physical examination, complete blood counts, and serum chemistries were monitored weekly during chemotherapy. Toxicity was evaluated for every course according to CTCAE version 3. Chest CT and other radiographic modalities necessary for evaluating target lesions by RECIST were repeated every 6 weeks until evident disease progression. Tumor response in every patient was evaluated by an external reviewer according to the RECIST, and was classified into four categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). A minimum of 6-week interval from the start of therapy was required for establishing SD.

2.5. Dose reduction and termination criteria of chemotherapy

The dose of docetaxel was reduced by 10 mg/m^2 every time one of the DLTs mentioned above was experienced; however, the reductions were not lower than 40 mg/m^2. Treatment was completely terminated when one of the following conditions was encountered: (1) patient's refusal, (2) serious adverse events, (3) disease progression, (4) inability to start the next course because of adverse events, (5) encountering one of the dose reduction criteria when the previous docetaxel dose was 40 mg/m^2, (6) low compliance of S-1 of less than 10 days out of 14 days on day 21, or (7) other conditions inappropriate for continuing treatment.