Combination Phase II Study of Weekly Paclitaxel and 5’-DFUR for Unresectable or Recurrent Gastric Cancer

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Abstract. Background: Paclitaxel and 5’-deoxy-5-fluorouridine (5’-DFUR) have single-agent activity in gastric cancer and have distinct mechanisms of action and no overlap of key toxicities. To evaluate the efficacy and safety of their combination, we conducted a combination phase II study of paclitaxel and 5’-DFUR in patients with unresectable or recurrent gastric cancer who had received up to one prior chemotherapy. Patients and Methods: Treatment included paclitaxel at 70 mg/m² i.v. on days 1, 8 and 15 every four weeks, and 5’-DFUR at 600 mg p.o. every day. The primary end-point was the response rate (RR) and secondary end-points were overall survival (OS), progression-free survival (PFS), time-to-treatment failure (TTF) and rate of adverse events. Results: In 42 eligible patients, the RR was 40.5%. OS, PFS and TTF were 371 days, 170 days, and 147 days, respectively. Adverse events were relatively mild. Commonly observed grade 3/4 adverse events were neutropenia (26.2%), anorexia (4.8%), neuropathy (4.8%) and fatigue (4.8%). Conclusion: The combination of weekly paclitaxel and 5’-DFUR chemotherapy is active and well-tolerated.

Gastric cancer is the fourth most common malignancy worldwide and the second leading cause of cancer-related death (1). Gastric cancer is moderately sensitive to systemic chemotherapy, which has been used in an attempt to control cancer-related symptoms and prolong survival. Previous randomized studies have shown that systemic chemotherapy can prolong survival and improve quality of life (QOL) (2-4). Among the various active chemotherapeutic agents, cisplatin-based chemotherapy is the one most commonly used worldwide. In Japan, after the results of the SPIRITS trial were published, S-1 plus cisplatin was accepted as a standard first-line treatment for patients with advanced gastric cancer (5). The V325 study demonstrated that a triplet regimen of 5-fluorouracil (5-FU), cisplatin and docetaxel (DCF) provided with clinical benefits and health-related QOL (6). Although the SPIRITS and DCF regimens provide with clinical advantages, these therapies are accompanied by an increase in toxicity and their toxicity profiles are acceptable only with appropriately selected patients and comprehensive toxicity management strategies (5, 7). In this regard, the development of less toxic combination chemotherapies is still considered necessary to properly treat patients with advanced gastric cancer.

Paclitaxel is one of the most active anticancer drugs for the treatment of solid tumors, effectively blocking cancer cells in the G2/M phase through the inhibition of microtubular depolymerization (8, 9). An administration schedule at doses of 175-225 mg/m² by intravenous infusion every three weeks has been widely accepted (10). Furthermore, recent clinical studies have demonstrated that weekly schedules of intravenous paclitaxel have promising anti-tumor activity with tolerable safety profiles for several types of solid tumors, including breast, ovarian and lung cancer (11-13).

5’-deoxy-5-fluorouridine (5’-DFUR), an active intermediate metabolite of capecitabine, is a pro-drug that is converted into 5-FU by thymidine phosphorylase (TYMP). A synergistic effect on inhibition of tumor growth has been reported when 5’-DFUR is combined with paclitaxel (14, 15). The results of a basic study demonstrated that administration of paclitaxel selectively induced TYMP in tumor tissues and that the combination of paclitaxel and 5’-
Concomitant use of these two drugs is expected to exert extra anti-tumor effects and to enhance the survival advantage, and can be regarded as a promising regimen for gastric cancer. In view of these beneficial effects, we conducted a phase II study in order to assess the efficacy of weekly paclitaxel and 5'-DFUR for patients with advanced gastric cancer.

Patients and Methods

Eligibility criteria. All eligible patients had to fulfill the following eligibility criteria: Histologically-confirmed unresectable or recurrent gastric cancer; over 20 years of age; Eastern Cooperative Oncology Group performance status (PS) 0-2; at least one measurable lesion according to the response evaluation criteria in solid tumors [RECIST version 1.0 (16)]; no prior chemotherapy or one prior chemotherapy excluding adjuvant setting; life expectancy ≥3 months; adequate bone marrow function (hemoglobin >9 g/dl, absolute neutrophil count ≥2,000/mm³ and platelet count ≥100,000/mm³); adequate liver function [total bilirubin ≤1.5 mg/dl and serum transaminase ≤2.5 × upper normal limit (UNL) (in cases of hepatic metastasis, ≤5 × UNL)]; adequate renal function (serum creatinine ≤1.5 × UNL); no other severe medical conditions; no other active malignancies; no history of paclitaxel or 5'-DFUR; and provision of written informed consent. The Institutional Review Board of each Author’s institution approved the protocol. The study protocol was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000008632).

Treatment schedule and evaluation of toxicity. We conducted a phase I clinical trial in order to study the feasibility of paclitaxel/5'-DFUR combined therapy (17). Based on the results, we determined the dose and schedule for this study. The two drugs were administered as follows: paclitaxel (Taxol; Bristol-Myers Squibb Company, Tokyo, Japan) at 70 mg/m² over 60 min by intravenous infusion on days 1, 8 and 15; 5'-DFUR (Futuron; Chugai Pharmaceutical Company, Tokyo, Japan) at 600 mg/day (400 mg/day, if body weight less than 40 kg) orally every day. This treatment was repeated every four weeks until disease progression or unacceptable toxicity was observed. Toxicity was graded according to the National Cancer Institute common toxicity criteria [NCI-CTC version 2.0 (18)]. Paclitaxel could be administered if the total leukocyte count was ≥3,000/mm³, neutrophil count was ≥1,500/mm³, the platelet count was ≥75,000/mm³ and all relevant non-hematological toxicities were grade 1 or lower. Treatment delay and dose reductions were planned for hematological or non-hematological toxicities as follows: at grade 2 to delay treatment for one week and to reintroduce paclitaxel at 70 mg/m² and 5'-DFUR at 600 mg/day; and at grade 3 to delay the treatment for one week and to reintroduce paclitaxel at 60 mg/m² and 5'-DFUR at 600 mg/day. The dose of paclitaxel could be reduced to 50 mg/m². Treatment could be withheld for up to two weeks. If adverse events did not improve to grade 1 after two weeks or grade 4 hematological or non-hematological toxicities were observed, patients were excluded from the study.

End-points and evaluation of treatment. The primary endpoint was the response rate (RR). Tumor response was evaluated every four weeks by means of computed tomography or magnetic resonance imaging. Measurable lesions were assessed according to RECIST version 1.0 (16). Secondary endpoints were overall survival (OS), progression free survival (PFS), time to treatment failure (TTF) and incidence of adverse events. Intention-to-treatment (ITT) analysis was used to evaluate patients for response, survival and toxicity.

Statistical analysis. Simon two-stage design was used (19). We hypothesized that our regimen would be effective if the RR reached 20%. Therefore, the present trial was designed to detect an RR of 40% as compared to a minimal, clinically meaningful response rate of 20%, with an alpha error of 0.05 and a beta error of 0.2. The required number of patients was estimated to be 38 and the total sample size was 42 patients allowing for a follow-up loss rate of 10%. OS, PFS and TTF were all estimated using the Kaplan–Meier method. TTF was defined as time from initiation of chemotherapy to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference or death. OS was measured from the initiation of chemotherapy to the date of the last follow-up or death. Data were analyzed statistically using the JMP software package (JMP 10.0.2; SAS Inc., Cary, NC, USA).

Results

Patients’ characteristics. Forty-two patients were enrolled in the trial between June 2004 and November 2006. The major clinicopathological characteristics of patients are listed in Table I. The median age was 70 years (range=44-85 years), with 34 males and 8 females. Out of the 42 patients, 40 had good performance status (ECOG 0 or 1). Twenty-nine patients had received no prior chemotherapy and 13 had received one prior course of chemotherapy (S-1 treatment). All had measurable disease according to the RECIST criteria (metastases in lymph
nodes in 26, liver in 19 and lung in two patients), and all were determined to be eligible for the present study.

**Anti-tumor activity.** According to ITT analysis, RR was 40.5% [17/42, 95% confidence interval (CI)=25.0-55.0%], including complete response (CR) in one and partial response (PR) in 16 patients. Seventeen patients showed stable disease (SD), disease in six patients progressed and response was not evaluable in two patients because of toxicity appearance during the first cycle of treatment. The disease control rate (PR+SD) was 81.0% (34/42) (Table II). RR was 48.3% (14/29) for first-line chemotherapy, and 23.1% (3/13) for S-1 failure second-line chemotherapy. The median survival time (MST) was 374 days (95% CI=299-455 days) (Figure 1). The median PFS was 170 days (95% CI=100-273 days) (Figure 2), and the median TTF was 151 days (95% CI=94-190 days) (Figure 3). The median follow-up period was 374 days (range=58-913 days). According to information from the off-treatment forms at the failure of this regimen, at least 21 out of 29 patients (72.4%) received second-line chemotherapy regimens, and eight out of 13 patients (61.5%) received third-line chemotherapy regimens.

**Toxicity.** The median number of treatment cycles was four (range 1-33). All patients were evaluable for toxicity. No toxic deaths were observed. Hematological toxicity was mainly presented by neutropenia that was recorded in 23 patients (55%), but grade 3-4 neutropenia appeared in 11 cases (26.2%). No patients experienced febrile neutropenia. Anemia was observed in only one patient (Table III). Non-hematological toxicity was uncommon. Two patients experienced grade 3 anorexia, fatigue and neuropathy. One patient experienced grade 3 diarrhea and stomatitis (Table IV). All patients received chemotherapy in an outpatient clinic.

**Discussion**

In this study, we showed that combination chemotherapy comprising of weekly paclitaxel and 5'-DFUR is an active regimen for patients with unresectable or recurrent gastric
cancer. The RR was 40.5% of patients, above the threshold of the minimal, clinically-meaningful RR (20%) and disease control was achieved in 81.0% of patients. The MST was 374 days and PFS was 170 days. Moreover, toxicity was not severe in our regimen. Grade 3-4 neutropenia developed in 26.2% of patients and grade 3-4 anorexia, fatigue and neuropathy developed in 4.8% of patients.

Many clinical trials of S-1 plus other chemotherapeutic agents such as cisplatin or docetaxel have been carried out in patients with advanced gastric cancer (5, 20). S-1 plus cisplatin is recognized as a standard treatment for patients with advanced gastric cancer in Japan following the results of the SPIRITS trial (5). The S-1 plus cisplatin regimen obtained an RR of 53% with OS of 13.0 months (5), while Van Cutsem et al. (6) reported an RR of 37% with OS of 9.2 months with DCF therapy in the V325 study. Many investigators reported that the RR ranged from 40 to 59% and the MST ranged from 9.0 to 12.0 months in patients treated with topoisoomerase I inhibitor- or taxane-based doublet (20). In this study, the RR was 40.5% and MST was 374 days. The RR in our study was comparable to those obtained in previous studies, and the MST in our study was equivalent or longer than those reported in previous studies. Regarding the anti-tumor effects, the present study showed promising results in patients with advanced gastric cancer.

The combination chemotherapy comprising of weekly paclitaxel and 5'-DFUR had very tolerable toxicities, as well as active anti-tumor effects. Hematological toxicities were not severe in this study, with only 26% of the patients experiencing grade 3-4 neutropenia. In addition, grade 3-4 fatigue and all grade 3-4 gastrointestinal toxicities, including anorexia, diarrhea and stomatitis developed in fewer than 5% of patients. Mild neurotoxicity could be attributable to the low dosage of weekly paclitaxel. In the SPIRITS trial, 40% and 30% of the patients experienced neutropenia and anorexia, respectively, and almost all patients needed short-term hospitalization for hydration to avoid renal toxicity caused by intravenous cisplatin (5). The final aim of cancer chemotherapy is to prolong the survival of patients, with good QOL. In particular, non-hematological toxicities substantially reduce patient QOL. Our study showed a low incidence of non-hematological toxicities, such as fatigue, anorexia, diarrhea and stomatitis, and this may have contributed to enhancing the OS without reducing QOL.

Two other phase-II studies of weekly paclitaxel in combination with 5'-DFUR for advanced gastric cancer have been reported. Takeyoshi et al. reported the results of a phase-II study of combination chemotherapy comprising of paclitaxel at 80 mg/m² intravenously on days 1, 8 and 15, every 4 weeks, and 5'-DFUR 533 mg/m² orally on days 1-5 every week for the patients with advanced gastric cancer who had received up to two prior courses of chemotherapy, and their regimen achieved the RR of 33.3% and MST of 287 days, with only 14% of grade 3-4 leucopenia (21). Takiuchi et al. reported the results of a phase-II study of combination chemotherapy comprising of paclitaxel at 80 mg/m² intravenously on days 1, 8 and 15, every 4 weeks, and 5'-DFUR 533 mg/m² orally on days 1-5 every week for the patients with advanced gastric cancer who showed resistance to S-1 (22). They reported that the RR was 18.2% and MST was 321 days, without severe hematological or non-hematological toxicities. In these studies, they used 80 mg/m² weekly paclitaxel, which was a higher dose than ours, and they used 5'-DFUR at a similar dose intensity as in our study. Both of these groups reported lower RRs and overall survival than us, as the incidence of patients with prior chemotherapy was higher than in our study. However, the low rate of adverse events was identical to ours.

In conclusion, the results of this phase-II study demonstrated that the combination of weekly paclitaxel plus 5'-DFUR was well-tolerated and effective, with a favorable toxicity profile. The present combination regimen at this schedule is an option for the treatment of patients with unsectectable or recurrent gastric cancer, particularly in second-line chemotherapy or for patients with recurrent disease who received adjuvant S-1 treatment.

**Conflicts of Interest**

The Authors have no conflicts of interest.
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References

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