Randomized Phase II Study Comparing Dose Escalated Weekly Paclitaxel vs. Standard Dose Weekly Paclitaxel for Patients with Previously Treated Advanced Gastric Cancer

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Weekly paclitaxel is an effective and widely used regimen for patients with advanced gastric cancer, with main dose-limiting toxicities of neutropenia and neurotoxicity. Neutropenia during weekly paclitaxel administration was reported to be associated with better survival. The aim of this study is to evaluate prospectively whether dosing adjustments based on the occurrence of neutropenia may improve chemotherapy efficacy. A total of 90 patients will be randomized to receive either a standard dose of weekly paclitaxel (80 mg/m2) or an escalated dose of weekly paclitaxel (80 mg/m2 initially followed by 100 and 120 mg/m2 unless severe toxicity is observed). The primary endpoint is overall survival. Secondary endpoints include progression-free survival, response rate, disease control rate and adverse events.

Key words: gastric cancer – chemotherapy – paclitaxel – neutropenia

INTRODUCTION

Paclitaxel is the most commonly used agent for second-line chemotherapy in advanced gastric cancer (AGC) in Japan (1,2). Although tri-weekly administration is the conventional schedule used for paclitaxel, weekly administration (dose-dense) was reported to be more effective and feasible in several types of cancer, with neutropenia as the most common schedule-limiting toxicity, with a severity of Grades 3–4 (3–5).

Neutropenia is a common adverse event with cytotoxic chemotherapy. In general, the recommended doses of cytotoxic agents are determined in dose-finding studies. However, the sample sizes in dose-finding studies are not large enough to examine individual differences in drug metabolism; therefore, toxicity profiles are likely to be highly variable (6). In other words, a standard dose may be insufficient to achieve efficacy for some patients with faster drug elimination times (6). In support of this hypothesis, toxicity such as neutropenia during chemotherapy has been reported to be associated with favorable clinical outcome in several types of cancer (7–15). Recently, we studied the effects of neutropenia occurring during second-line chemotherapy with weekly paclitaxel in a retrospective analysis of 242 patients with AGC (15). Of the 242 patients, mild neutropenia (Grades 1–2) occurred in 101 patients (41.7%) and severe neutropenia (Grades 3–4) occurred in 63 patients (26.0%). The other 78 patients (32.2%) did not experience neutropenia. The median overall survival times in the absent group, mild group and severe group were 3.9, 8.8 and 8.1 months, respectively. According to a multivariate Cox model with neutropenia as time-varying covariates, hazard ratios of death were 0.61 [95% confidence interval (CI): 0.43–0.85; P = 0.004] for patients with mild neutropenia and 0.61 (95% CI: 0.41–0.88; P = 0.009) for those with severe neutropenia. Among the patients in landmark analysis (landmark of 2.5 months; median time-to-treatment failure of paclitaxel), mild and severe neutropenia remained significant prognostic factors (15).
Our results, in addition to those of other reports, consistently showed that patients experiencing neutropenia during chemotherapy had better prognoses compared with patients who did not experience neutropenia as shown in our meta-analysis (16). These results might suggest that neutropenia is a surrogate marker for adequate antitumor doses of chemotherapeutic agents. However, to the best of our knowledge, no study has evaluated prospectively whether dosing adjustments based on neutropenia may improve chemotherapy efficacy. Therefore, we have planned a randomized phase II study comparing dose escalated weekly paclitaxel according to neutropenia vs. standard dose weekly paclitaxel for patients with previously treated AGC.

DIGEST OF THE STUDY PROTOCOL

PURPOSE

The aim of this randomized phase II screening study is to evaluate the efficacy of dose escalated weekly paclitaxel to determine whether this treatment is promising in comparison with the standard dose of weekly paclitaxel for the treatment of patients with AGC that has progressed after one or more prior chemotherapy regimens.

STUDY SETTING

This is a multi-institutional, open-label, randomized, phase II trial, for which, as of August 2010, planned participating institutions include 12 specialized centers.

ENDPOINTS

The primary endpoint is overall survival. Secondary endpoints include objective response rate, disease control rate, progression-free survival and adverse events.

INCLUSION CRITERIA

Prior to enrollment in the study, patients must fulfill all of the following criteria: (i) presence of histopathologically or cytologically proven unresectable or recurrent gastric adenocarcinoma; (ii) presence of radiographically confirmed or clinically diagnosed disease progression during one or more previous chemotherapy regimens or recurrence within 6 months after the last adjuvant chemotherapy dose; (iii) Eastern Cooperative Oncology Group performance status (PS) 0–2; (iv) age 20 or older; (v) presence of evaluable disease; (vi) adequate bone marrow reserve (leukocyte count ≥3000/mm$^3$; neutrophil count ≥1500/mm$^3$; hemoglobin level ≥8.0 g/dl, platelet count ≥100 000/mm$^3$); (vi) adequate hepatic function [aspartate aminotransferase and alanine aminotransferase <100 IU/l (<200 IU/l in patients with liver metastases) and total bilirubin <1.5 mg/dl]; (vii) adequate renal function (serum creatinine <2.0 mg/dl).

EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria: (i) previous history of chemotherapy including taxanes (e.g. paclitaxel, docetaxel, etc.); (ii) uncontrollable ascites or pleural effusion; (iii) serious comorbidities, such as pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes mellitus, severe heart disease, other active malignancy, active inflammation or other serious medical conditions.

PATIENT ASSIGNMENT

The Data Center (Division of Epidemiology and Prevention of Aichi Cancer Center Research Institute) will confirm patient eligibility and treatment will be assigned automatically according to the stratifying factors for eligible patients. The following three variables will be used for stratification: PS (0–1 vs. 2), measurable lesion (present vs. absent) and number of previous treatment regimens (1 vs. 2 or more). Entered patients will be assigned randomly to receive a standard dose of weekly paclitaxel (control arm) or an escalated dose of weekly paclitaxel (experimental arm).

TREATMENT METHODS

In the control arm, paclitaxel will be administered at a starting dose of 80 mg/m$^2$ intravenously (i.v.) over the course of 1 h weekly on Days 1, 8 and 15 for each 4-week period, as reported previously (1,2).

In the experimental arm, paclitaxel will be similarly administered at a starting dose of 80 mg/m$^2$ i.v. over the course of 1 h. Then, if patients do not experience Grades 2–4 neutropenia (neutrophil count <1.5 × 10$^9$/l) or severe toxicity, the dose of paclitaxel will be increased to 100 mg/m$^2$ on Day 8. Similarly, the dose will be further escalated to 120 mg/m$^2$ on Day 15 if no toxicity or neutropenia is present. No dose escalation will be permitted after Day 15. The treatment will be continued with 3 successive weekly infusions and 1 week of rest, as for the control arm.

Patients will receive premedication with antihistamine (e.g. diphenhydramine hydrochloride 50 mg), dexamethasone 8 mg and cimetidine 300 mg (or a comparable H2 blocker) to minimize the risk of hypersensitivity reactions associated with paclitaxel.

Chemotherapy will be delayed until recovery for a neutrophil count <1.0 × 10$^9$/l, a platelet count <5.0 × 10$^9$/l or any significant persisting nonhematologic toxicity. For Grade 4 neutropenia lasting more than 1 week, febrile neutropenia, Grade 4 thrombocytopenia or Grade 3 neuropathy or other non-hematological toxicity, the paclitaxel dose will be reduced by 20 mg/m$^2$ in both arms.
Treatment will be discontinued if the tumor progresses, severe toxicity occurs or requested by the patient. There is no set maximum number of administrations.

Prophylactic use of granulocyte-colony-stimulating factor (G-CSF) is not permitted, and G-CSF is generally recommended in cases of Grade 4 neutropenia or febrile neutropenia.

**FOLLOW-UP**

Physical examinations, safety evaluations and laboratory tests will be performed prior to treatment initiation and weekly thereafter. Responses will be evaluated every 8 weeks or earlier if there are indications of treatment failure due to toxicity. All eligible subjects will be included in the assessment of efficacy and safety. Nonevaluable subjects will be added into the efficacy assessment data set as ‘not evaluable.’ The following dates will be recorded: (i) date of starting treatment, (ii) date of disease progression, (iii) final date assessing survival and (iv) date of death.

**STUDY DESIGN AND STATISTICAL METHODS**

The study is designed as a randomized screening phase II trial with a one-sided alpha of 0.3 with a power of 0.80. The primary endpoint is overall survival. The assumed median survival time (MST) with the standard regimen is 5 months in this heavily pretreated patient population, and the expected survival benefit is 2 months (MST of 7 months in the experimental arm). The sample size is calculated as 90, with planned accrual in 1 year.

Overall survival will be estimated from the date of study entry to the date of death or last follow-up visit based on Kaplan–Meier methodology. Progression-free survival will be measured from the date of entry into the trial to the time when progression or death without evidence of progression occurs. The tumor response will be assessed objectively after each course, according to the Response Evaluation Criteria in Solid Tumors version 1.1. Adverse events will be evaluated with the Common Terminology Criteria for Adverse Events version 4.0.

**INTERIM ANALYSIS**

The Data and Safety Monitoring Committee (DSMC) will independently review the report of trial monitoring regarding the efficacy and safety data from the present study. Since no feasibility study of dose escalation was performed prior to this study, an interim analysis especially for safety will be performed after the registration of 20 patients (10 patients in each arm). On the basis of the results of this interim analysis, the DSMC can consider early termination of a treatment regimen during the study or modification of the study protocol if there is unexpected high number of toxicity-related death.

**REGISTRATION OF THE PROTOCOL**

The study protocol was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000004055) on 1 June 2006. Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000004871&language=E

**Conflict of interest statement**

None declared.

**References**

