A phase I/II clinical trial has been planned to evaluate the safety and efficacy of combination therapy of S-1 with low-dose cisplatin in patients with unresectable or recurrent gastric cancer. A new statistically as well as clinically deliberated study design is applied to determine the maximal benefits of combination chemotherapy. This trial uses a ‘continual reassessment method’ for evaluating toxicity and a ‘two-stage method’ for assessing the response rate to determine the combination that achieves adequate tumor response without toxicity in a high proportion of patients. Three specialized institutions will recruit 10–16 patients for the phase I part of the trial, and 14 institutions, in conjunction with the three specialized ones, will enroll 42 patients for the phase II part. The goal of this trial is to establish a useful chemotherapeutic treatment in an outpatient setting.

Key words: S-1 – low-dose cisplatin – continual reassessment method – gastric cancer – phase I/II trial

INTRODUCTION

Treatment using S-1 is not only convenient as it allows oral drug administration, but has also demonstrated higher efficacy and safety in patients with unresectable and/or recurrent advanced gastric cancer. Therefore, S-1 has been recognized as one of the standard treatments currently used in Japan (1–3). To establish a more effective treatment regimen while minimizing the occurrence of adverse events, combination therapy with S-1 and various drugs has been examined. Beginning in February 2000, the Japanese Foundation for Multidisciplinary Treatment of Cancer started an initiative to carry out a phase I clinical trial evaluating the safety of combination therapy of S-1 with low-dose cisplatin, five times per week (4). This dose escalation study for cisplatin (1 mg/m², 2 mg/m², 3 mg/m², 4 mg/m², and 6 mg/m², designated levels 1–5), determined the maximum tolerated dose (MTD) to be level 5 and, consequently, level 4 (cisplatin 4 mg/m², 5 days/week) was set as the recommended dose. However, this regimen with its schedule of administering cisplatin five times per week requires a longer hospitalization (since cisplatin is usually administered in hospital), and therefore implementation of a phase II clinical trial using this regimen was not considered feasible in the current medical and economic environment in Japan. For this reason, after completion of the phase I study, a new study, applicable on an outpatient basis, was deemed necessary as a phase I/II clinical trial to determine a twice-a-week cisplatin administration schedule. To set up a protocol administering cisplatin in a twice-a-week schedule, we used information obtained in the phase I clinical trial and adopted a continual reassessment method (5,6) to estimate a recommended dose for new scheduling and dosing. In contrast to a phase I trial, where a dose escalation study is conducted to find the MTD, in this new trial we aim to establish a regimen with higher efficacy while minimizing adverse effects. Therefore, when advancing from phase I to phase II, we have decided to implement an interim analysis and monitoring to report not only toxicological assessment but also the efficacy and anti-tumor effects of combination therapy.

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PROTOCOL DIGEST OF THE STUDY

PURPOSE
To evaluate the safety of a newly scheduled combination therapy of S-1 with low-dose cisplatin in patients with unresectable or recurrent gastric cancer, to determine the recommended dose (RD) and MTD, and to examine the efficacy of the treatment regimen at the RD.

STUDY SETTING AND PROTOCOL REVIEW
Open-label, phase I/II clinical trial. The protocol was approved by the Protocol Review Committee of the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC). Supported by Research Grants from the JFMC, Japan

ENDPOINTS
Primarily, objective tumor response and adverse events. Secondly, alterations in tumor markers, pharmacokinetics of cisplatin and survival. Tumor response is reviewed extramurally. Adverse events are evaluated according to the National Cancer Institute: Common Toxicity Criteria version 2.0.

ELIGIBILITY CRITERIA
Patients with a histologic diagnosis of unresectable or recurrent gastric cancer are eligible.

INCLUSION CRITERIA
- Histologically demonstrated advanced gastric cancer.
- Measurable or assessable disease.
- Age range from 20 to 75 years.
- No anti-tumor therapy within 28 days prior to enrollment.
- ECOG performance status (PS) 0 to 1.
- Life expectancy longer than 12 weeks.
- Adequate bone marrow function (Hb \( \geq 9.0 \) g/dl, white blood cells between 4000 and 12 000/µl, platelets \( \geq 100 000/\mu l \)).
- Sufficient organ function.
- Written informed consent.

EXCLUSION CRITERIA
- Any cases with severe complication(s).
- Any cases with symptomatic brain metastases.
- Any cases with active double cancers.
- Any women who are currently pregnant, nursing, or plan to become pregnant.
- Any other cases where the investigator disapproves of participation in this clinical trial.

REGISTRATION
Eligibility criteria checking report form will be made at each site, and the JFMC Data Center will confirm the above criteria. Patients are then registered.

TREATMENT METHODS
S-1 is administered orally twice daily after a meal at one of three initial doses based on body surface area (BSA): (i) BSA \(<1.25 \text{ m}^2\), 80 mg/day; (ii) \(1.25 \text{ m}^2 \leq \text{BSA} <1.5 \text{ m}^2\), 100 mg/day; and (iii) \(1.5 \text{ m}^2 \leq \text{BSA}, 120 \text{ mg/day}\). One cycle consists of consecutive administration for 28 days followed by 14 days rest. Low-dose cisplatin in 100 ml of normal saline as a 1-h intravenous injection is given twice a week for four weeks, that is, on days 1, 4, 8, 11, 15, 18, 22 and 25, followed by two weeks rest in each cycle. Consecutive cycles of combination therapy should continue for at least two cycles. Patients should remain in the study until (i) the occurrence of dose-limiting toxicities (within the first cycle), or grade 4 hematological or grade 3 and 4 non-hematological toxicities (after the first cycle), (ii) the appearance of objective evidence of tumor progression or (iii) it is no longer in the patient’s best interest to continue.

Three dose levels will be scheduled for cisplatin: level 1, 7.5 mg/m²/day; level 2 (starting dose), 10 mg/m²/day; and level 3, 15 mg/m²/day. These doses and the starting dose were established in light of data from a previously conducted phase I trial (4). Discontinuation of therapy should be based on hematologic toxicities including grade 2 or greater leukopenia, neutropenia and thrombocytopenia, grade 2 or greater non-hematologic toxicities (except alopecia), and a deterioration in PS of 2 or more during each treatment cycle. In cases where therapy is discontinued, physicians should confirm that patients have recovered from toxicity prior to resuming treatment. If the toxicity causing treatment discontinuation is grade 3 or greater leukopenia, neutropenia, or grade 2 or greater thrombocytopenia, the dose of S-1 should be reduced from 80, 100 and 120 mg/day to 50, 80 and 80–100 mg/day, respectively. The dose of cisplatin should not be modified during the first and second cycles.

DEFINITION OF DOSE LIMITING TOXICITY
Dose limiting toxicity (DLT) is defined as the occurrence of any of the following observed within the first cycle of treatment: (i) grade 3 and 4 leukopenia for 3 days or more; (ii) grade 3 and 4 neutropenia along with fever (febrile neutropenia); (iii) grade 3 and 4 thrombocytopenia; (iv) grade 3 or greater non-hematologic toxicity, excluding alopecia, nausea/vomiting and general fatigue; (v) total treatment interruption lasting more than 3 weeks; or (vi) patient’s refusal to continue treatment due to adverse events or related matters.

FOLLOW-UP
Patients are seen by their physicians twice a week before cisplatin injection. Abdominal computed tomography, ultrasonography or upper gastrointestinal series are performed at baseline and after every treatment cycle. Blood tests are carried out before treatment and at least once a week during treatment. Symptoms such as anorexia, nausea/vomiting, stomatitis and diarrhea are also surveyed.
STUDY DESIGN AND STATISTICAL METHODS

This phase II trial is designed to examine a series of two questions in the phase I and phase II parts. The objective of phase I is to determine the RD level of cisplatin in combination with S-1 at which patients enrolled into phase II will be treated. The objective of the phase II part is to estimate the response rate of combination therapy at the RD determined in the phase I part.

Evaluation of the RD is performed using a likelihood approach continual reassessment method (CRML) proposed by O’Quigley and Shen (6). The target toxicity level of the CRML to estimate the RD is set at 20%. In other words, the RD of this study is determined as that closest to a dose level at which 20% of patients would experience DLT. The MTD is defined as that closest to a dose level at which 33% of patients would experience DLT. In CRML calculations, sensitivity analysis for parameters in a dose-toxicity model will be applied, instead of using a prior distribution for the model parameters. This trial sets possible toxicity levels of dose levels 1, 2 and 3 at 5–30%, 10–40% and 20–70%, respectively. The starting dose level in this trial is level 2, with the first two enrolled patients (first patient cohort) treated at this level. After enrollment of the first cohort, we sequentially include a new patient cohort after observing DLT data during the first treatment cycle in the cohort of previously treated patients. Dose escalation and de-escalation determination for consecutive patient cohorts is based on CRML calculations and clinical judgment. Skipping from level 1 to level 3 is not allowed in the CRML calculations. The size of each cohort is also based on CRML calculations. For example, the size of a cohort becomes two when there are two candidates to be included successively over a short time period, such as two or three weeks, and the RD for the latter patient does not change regardless of whether the former patient experiences DLT or not. In addition, inclusion of more than three patients in one cohort is not allowed. Taking the simulation studies performed by O’Quigley and Shen (6) into account, the phase I part is expected to require 10–16 patients.

During the phase II part, estimation of response rate at the RD is performed and follow-up examination of toxicity level is done using CRML to reconfirm the safety of the RD. The required sample size for the phase II was estimated to be 39 at 10% type I and type II errors and under the assumption of 40% and 60% response rates for the null and alternative hypotheses, respectively. Taking inevaluable patients into account, the sample size was set at 42.

The phase I part of this trial will be completed, and the phase II part will be started, when clear separation of the confidence intervals for the three dose levels appears. This decision will also be made according to clinical judgment. In case the selected regimen at the RD is considered insufficiently active at the end of the phase I part, this trial will be terminated. In other words, the trial will be halted when the hypothesis that the response rate at the RD is over 60% is rejected with a statistical test (7).

INTERIM ANALYSIS AND MONITORING

The Individual Data and Safety Monitoring Committee (IDSMC) will independently review the report of interim analysis regarding phase I data and can consider stopping the trial early. Protocol compliance, safety and on-schedule study progress are also monitored by the IDSMC.

PARTICIPATING INSTITUTIONS

Sapporo Tsukisamu Hospital (Department of Surgery), Doto Hospital (Department of Surgery), Asahikawa Kousei Hospital (Department of Surgery), Sendai Kousei Hospital (Department of Gastroenterology and Medical Oncology), Fukusima Medical University (Department of Surgery I), Kizawa Memorial Hospital (Department of Surgery), Nagoya National Hospital (Department of Surgery), Osaka University Graduate School of Medicine (Laboratory of Molecular and Cellular Recognition), Osaka City University Graduate School of Medicine (Department of Surgical Oncology), Saiseikai Senri Hospital (Department of Surgery), Osaka National Hospital (Department of Surgery), Sumitomo Hospital (Department of Surgery), Wakayama Medical University (Second Department of Surgery, School of Medicine), Tottori University (Department of Surgery, Division of Surgical Oncology, School of Medicine), Kochi Municipal Central Hospital (Department of Internal Medicine), Nagasaki University Graduate School of Biomedical Sciences, Kumamoto Rosai Hospital (Department of Surgery).

References