A Randomized Phase II Clinical Trial of Tailored CPT-11 + S-1 vs S-1 in Patients with Advanced or Recurrent Gastric Carcinoma as the First Line Chemotherapy

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INTRODUCTION

A standard chemotherapy for advanced gastric cancer has not yet been established worldwide. In Japan, to date, no chemotherapeutic agent or combination of agents better than continuous infusion of 5-FU (5FUci) have been reported in any relevant clinical trials (1). Therefore, the 5FUci regimen is still regarded as the most acceptable reference arm in Japanese randomized clinical trials for advanced gastric cancer. In 1999, however, a new anticancer drug S-1 was developed (2), which has been expected to be a potentially promising agent for gastric cancer. Response rates of S-1 in two Japanese late phase II clinical trials for advanced gastric cancer were 53.6% (3) and 44.6% (4,5). It has been reported that S-1 induced complete remission even in 5-FU resistant cases (6). Moreover, phase II clinical trials of combination chemotherapy with S-1 and other drugs are on-going. Among these trials, phase I/II clinical trials of CPT-11 + S-1 have shown a response rate of greater than 50% with tolerable toxicity (7,8). Reduction of thymidylate synthase (TS) gene expression by CPT-11 has been reported (9), and a positive correlation between topoisomerase-I and TS has been suggested as a mechanism of the synergistic effect of the combination of these two chemotherapeutic agents (10,11).

In certain patients, however, severe toxicities even at a much lower dose than the maximum tolerated dose (MTD) have been observed in general clinical practices of the CPT-11/S-1 combination therapies. In order to reduce the considerably high toxicity of this regimen, we have proposed a tailored dose chemotherapy (12,13) in order to improve compliance, prolong the drug administration period and eventually prolong survival.

Comparison of this tailored dose CPT-11/S-1 combination with the standard S-1 administration in this randomized phase II trial will be utilized for the selection of one of the best candidate treatment arms for a future large scale randomized phase III study that will be performed by placing 5FUci as the reference arm.
PROTOCOL DIGEST OF THE STUDY

PURPOSE
To select the better treatment between tailored CPT-11/S-1 arm and the standard S-1 chemotherapy arm as the first line treatment for advanced/recurrent gastric cancer patients, and to investigate which one of the two regimens is a better candidate for a future phase III randomized trial, as compared to 5FUci treatment.

The trial is an open-label, randomized controlled phase II clinical trial. The protocol was approved by the Protocol Review Committee of the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC).

RESOURCES
Research grants from the JFMC.

ENDPOINTS
Primarily, response rate (RR). Secondarily, time to progression (TTP), time to treatment failure (TTF), survival, toxicity and compliance.

ELIGIBILITY CRITERIA
Tumors should be staged according to the UICC classification of gastric carcinoma. Patients with advanced or recurrent gastric cancer, who have not received any chemotherapy except oral or parenteral fluorinated pyrimidines (excluding S-1) as an adjuvant chemotherapy, are eligible for the trial.

INCLUSION CRITERIA
1. Histologically demonstrated adenocarcinoma of the stomach
2. Failed operation or recurrence of gastric cancer
3. Measurable or assessable lesions
4. No prior therapy including radiation and/or chemotherapy except adjuvant chemotherapy after the preceding curative resection
5. Age ranging from 20–74 years
6. Expected survival over 12 weeks
7. ECOG performance status 0–1
8. Sufficient organ functions
9. Written informed consent

EXCLUSION CRITERIA
1. History of using S-1
2. Medical history of allergy or hypersensitivity reactions to any drug
3. Serious effusion of cancerous fluids such as pleural effusion and/or ascites
4. Serious infectious disease
5. Diarrhea
6. Ileus or colon dysfunction
7. Lung fibrosis
8. Intake of flucitosine
9. Synchronous or metachronous or other types of malignancies
10. Uncontrollable diabetes mellitus
11. Serious heart disease
12. Serious psychological disease
13. Pregnancy
14. Patients judged inappropriate for this study by the physicians

REGISTRATION
Eligibility criteria checking report form will be sent to the JFMC Data Center after confirmation of the above criteria. Patients will then be allocated using dynamic randomization and registered either into Arm A or B. Information regarding the necessary follow-up examinations and recommended chemotherapy schedule will then be sent from the Data Center.

TREATMENT METHODS
Arm A: CPT-11 (75 mg/m²) was administered biweekly as one-hour intravenous infusion for 4 weeks (one cycle). If the manifested toxicity (excluding diarrhea) defined by NCI-CTC criteria was found to be 0 or 1 during the first cycle, the dose of CPT-11 will be increased by 25 mg/m² raising the total dose to 100 mg/m². If grade 2 toxicity is observed, the same dose will be maintained, and if toxicities of grade 3 and more are observed, the dose of CPT-11 will be decreased by 25 mg/m², reducing the dose to 50 mg/m² for the second cycle. The dose adjustment will be repeated in every cycle in the same manner.

A starting dose of 75 mg/m² of CPT-11 was determined on the basis of the MTD (125 mg/m²) and the recommended dose (100 mg/m²) defined by the previous phase I/II studies on the combination CPT-11 and S-1 therapy (7).

S-1 was administered in one of the following doses twice daily, after breakfast and dinner; body surface area (BSA) <1.25 m², 40 mg; 1.25 m² < BSA < 1.50 m², 50 mg; BSA ≥1.5 m², 60 mg. S-1 was administered at the respective dose for 14 days, followed by a 14-day rest period (one cycle). Dose reduction will be performed with the same criteria as the original S-1 administration schedule as followed in Arm B. The dose adjustment will be repeated in every cycle in the same manner.

Arm B: Single-agent S-1 was administered in the same dose as that in Arm A, and for 28 days, followed by a 14-day rest period (one cycle), which is the original schedule defined by a phase I study on S-1.

FOLLOW-UP
Patients should be examined by their physicians every week before the administration of CPT-11 or/and S-1. Measurements of the size of the lesions are performed by imaging techniques such as CT every 4 weeks. The physician should record the data including toxicity and report to the Data Center every 4 weeks.
STUDY DESIGN AND STATISTICAL METHODS

The sample size was estimated to be 37 to select the better treatment with probability $P = 0.90$ based on the expectation that a 15% difference will be observed in the response rates between the two arms (14). Taking ineligible patients into account, the sample size was set at 45 for each arm.

SUBSIDIARY ANALYSIS FOR THE TAILORED THERAPY

A relevant clinical trial of tailored dose chemotherapy has not been reported, except in an adjuvant chemotherapy trial for breast cancer (12). In order to examine the exploitability of the tailored dose chemotherapy for gastric cancer, we have designed this randomized phase II trial, placing the tailored therapy arm in the prospective study.

We have previously developed and proposed a new dose-finding system, ‘the individualized maximum repeatable dose (iMRD)’ (13), and achieved longer survival with less toxicity in 18 pancreatic cancer patients. It is of special interest whether our weekly dose adjustments using a maximum dose-limiting toxicity of grade 2 or 3 have any correlation with the enzymatic and pharmacokinetic characteristics of the individual patients in the present prospective trial.

To examine the effect of the tailored dose therapy, a subsidiary pharmacokinetic (PK) study was suggested in patients after a strict informed consent was obtained. We proposed to evaluate several factors such as Cmax, Tmax, AUC_{0-24} of SN-38 and SN-38g as PK of CPT-11, and AUC_{0-24}, AUC_{0-\infty}, t_{1/2} of FT, 5-FU, OxO, CDHP as PK of S-1 at the first cycle and the third cycle.

By analyzing the above data, we expect to elucidate the correlation between the PK of these drugs at the first cycle and adjustment dose (dose at third cycle), and compare the PK of these drugs at the third cycle in every adjustment dose, which is thought to be the individual optimal dose.

PARTICIPATING INSTITUTIONS

Approximately twenty out of fifty leading Japanese institutions and hospitals are expected to participate and enroll patients into this trial: Hokkaido University Graduate School of Medicine (Internal Medicine, Gastroenterology and Hematology), Sapporo Medical University School of Medicine (Surgery), Asahikawa Medical College (Surgery II), National Sapporo Hospital, Sapporo Social Insurance General Hospital (Surgery), Sapporo Tukisamu Hospital, Sapporo Memorial Hospital of Surgery, Hokkaido Gastroenterology Hospital, Nikko Memorial Hospital, Asahikawa Kosei Hospital, Kushiro Rosai Hospital (Internal Medicine), Doto Hospital (Surgery), Aomori Prefectural Central Hospital (Gastroenterology), Hiroaki University School of Medicine (Surgery II), Iwate Medical University (Surgery I), Senseki Hospital, Saitama Medical School (Surgery II), Chiba Cancer Center (Clinical Oncology), Showa University School of Medicine (Surgery II), National Tokyo Medical Center, Keio University School of Medicine (Surgery), Kitasato Institute Hospital (Surgery), Tokyo Medical University, Kanazawa University School of Medicine (Surgery Oncology), Fuku Red Cross Hospital, Gifu Municipal Hospital (Surgery), Kizawa Memorial Hospital, Hakuiakai Hospital, Aichi Cancer Center (Gastroenterological Surgery), Nagoya City University Graduate School of Medical Sciences (Gastroenterological Surgery), Aichi Medical University, Osaka City General Hospital (Gastroenterological Surgery), NTT West Osaka Hospital, Osaka City University Graduate School of Medicine (Surgical Oncology), Saiseikai Senri Hospital, Osaka Medical College (General and Gastroenterological Surgery), Osaka Minami National Hospital, Tondabayashi Hospital (Surgery), Hyogo Prefectural Nishinomiya Hospital, Hyogo Medical Center for Adults, Kansai Rosai Hospital, Tottori University Faculty of Medicine (Surgical Oncology), Okayama University Graduate School of Medicine and Dentistry (Gastroenterological Surgery), Hiroshima University Research Institute for Radiation Biology and Medicine (Surgical Oncology), The Institute of Gastroenterology of Bofu (Digestive Surgery and Surgical Oncology), Yamaguchi University School of Medicine (Digestive Surgery and Surgical Oncology), Kochi Municipal Central Hospital, Saiseikai Kumamoto Hospital and Kumamoto City Hospital.

References


