

# Feasibility Study of Bolus 5-Fluorouracil+L-Leucovorin as Salvage Line Chemotherapy for Oral Fluorouracil-Resistant Unresectable Gastric Cancer: Hokkaido Gastrointestinal Cancer Study Group Study HGCSG1502

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## Abstract

In November 2015 we began a feasibility study of salvage line chemotherapy with 5-fluorouracil and l-leucovorin given in an intravenous bolus once weekly followed by a 2-week rest period within a 8-week cycle in patients with gastric cancer resistant to other chemotherapies. This study aims to assess the safety and efficacy of this treatment and determine whether the treatment has an adverse effect on patients' quality of life. In total, 38 patients with chemotherapy-resistant advanced or recurrent gastric cancer will be recruited to this study. The primary end point is 8-week progression-free survival after the date of first treatment; the major secondary end points are progression-free survival, overall survival, and quality of life assessed by European Organization for Research and Treatment of Cancer QLQ-C30 (quality of life score-30) and QLQ-STO22 (quality of life for gastric cancer patients) questionnaires. Based on the results of the study, we will conduct further trials to compare this treatment with best supportive care only.

**Keywords:** Gastric cancer; Chemotherapy; 5-Fluorouracil; Leucovorin

## Introduction

In Japan, the prevalence of gastric cancer, the second most common malignancy nationwide, continues to increase every year. Gastric cancer accounted for about 133,000 active cases and about 49,400 deaths in 2015. According to the results of the JCOG9205 study [1], 5-fluorouracil (5-FU) is not inferior to and is less toxic than 5-FU +cisplatin and tegafur+uracil+mitomycin C. The subsequent JCOG9912 study [2] that compared 5-FU vs. irinotecan and cisplatin vs. monotherapy with S-1, which is an oral-fluorouracil agent, found no significant inferiority to either 5-FU monotherapy or irinotecan +cisplatin; therefore, S-1 monotherapy was adopted as the standard therapy for unresectable or recurrent gastric cancer. The SPIRITS trial [3] showed that progression-free survival (PFS) and overall survival

(OS) with S-1+cisplatin combination therapy were significantly superior to PFS and OS with S-1 monotherapy; therefore, S-1+cisplatin combination therapy was established as the standard primary chemotherapy for unresectable or recurrent gastric cancer in Japan. In contrast, the REAL-2 [4] and G-SOX [5] studies found that oxaliplatin was non-inferior to cisplatin and that it can replace cisplatin for treatment of gastric cancer. Further, the ToGA trial [6,7] reported that the addition of trastuzumab to 5-FU+cisplatin or capecitabine +cisplatin improved OS of patients with gastric cancer with the overexpression of human epidermal growth factor receptor 2, whereas the RAINBOW [8,9] and REGARD [10] trials found that ramucirumab, which is a humanized antibody against vascular endothelial growth factor, prolonged OS of patients with gastric cancer treated with and without paclitaxel. After the development of resistance to first-line chemotherapy, docetaxel or irinotecan, as second-line chemotherapy, can prolong OS, as compared with best supportive care alone [11]. However, there is not a negligible number

of patients with gastric cancer resistant to both of these chemotherapy regimens who will require further chemotherapy.

The ISO-5FU10 study [12] reported that the efficacy of weekly bolus 5-FU+l-leucovorin therapy was not inferior to that of S-1 monotherapy, which was the standard first-line chemotherapy for unresectable advanced gastric cancer in Japan at that time. There are two known mechanisms underlying the anticancer effects of 5-FU [13,14]. One is the inhibition of DNA synthesis through inhibition of thymidylate synthase activity by fluorodeoxyuridine-5'-monophosphate, a metabolite of 5-FU; the second mechanism is inhibition of RNA dysfunction by 5-fluorouridine triphosphate, another metabolite of 5-FU. Since inhibition of DNA synthesis by 5-FU is mainly time dependent, continuous infusion of 5-FU or daily administration of oral fluoropyrimidine drugs, such as S-1 and capecitabine, exerts an antitumor effect. However, the antitumor effect of RNA dysfunction by rapid injection of 5-FU is concentration dependent. Thus, bolus 5-FU+l-leucovorin therapy is expected to be effective against oral fluoropyrimidine-resistant gastric cancer. In fact, our single-centered retrospective analysis [15] reported that the median OS time was 6.3 months, which was numerically longer than that previously reported for placebo treatment [10,16].

This study will assess the efficacy of bolus 5-FU+l-leucovorin for oral fluoropyrimidine-resistant unresectable gastric cancer.

## Protocol Digest of HGCSG1502

### Purpose

The purposes of the study are to assess the safety and efficacy of bolus 5-FU+l-leucovorin for the phase III studies, comparing best supportive care only with current standard therapy, and to determine whether the treatment has an adverse effect on patients' quality of life.

### Study setting

A phase II, prospective, multicenter (18 centers), single-arm trial.

### End points

The primary end point is the 8-week PFS rate.

The secondary end points are (1) overall response rate (ORR); (2) disease control rate (DCR); (3) OS; (4) PFS; (5) time to treatment failure (TTF); (6) dose intensity and relative dose intensity; (7) adverse events; (8) patients' quality of life, evaluated by the European Organization for Research and Treatment of Cancer QLQ-C30 (quality of life score-30) and QLQ-STO22 (quality of life for gastric cancer patients) questionnaires [17,18].

### Eligibility criteria

**Inclusion criteria:** The study subjects are patients with a diagnosis of unresectable advanced, metastatic, or recurrent gastric cancer, which have had resistance of S-1 or capecitabine, and had resistance or intolerance of cisplatin or oxalilatin, paclitaxel or docetaxel, irinotecan, and ramucirumab. The further inclusion criteria are (1) 20 years of age or older; (2) Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2; (3) Adequate organ functions, as follows: neutrophil count  $\geq 1200/\text{mm}^3$ , platelet count  $\geq 75,000/\text{mm}^3$ , alanine amino transferase (ALT)  $\leq 3 \times$  upper limit of normal of the study site (ALT  $\leq 5 \times$  ULN of the study site in patients with liver metastases), total bilirubin  $<2.0$

mg/dl, and serum creatinine  $<2.0$  mg/dl; and (4) Written informed consent.

**Exclusion criteria:** (1) Active advanced double cancer; (2) Uncontrollable active infection, diarrhoea, diabetes mellitus, or ascites; (3) Intestinal obstruction; (4) Pulmonary fibrosis; (5) Undergoing treatment with flucytosine; (6) Undergoing radiation therapy; and (7) previous treatment with bolus 5-FU+l-leucovorin.

### Treatment

The treatment is l-leucovorin 250 mg/m<sup>2</sup>/2 h div and 5-FU 600 mg/m<sup>2</sup> iv bolus given intravenously once weekly followed by a 2-week rest period, within a 8-week cycle. The treatment cycles are repeated every 8 weeks with best supportive care until tumor progression or intolerable toxicity occurs.

### Study Design and Statistical Methods

This study is conducted as a single-armed safety and efficacy study. Thirty-four patients are required for an expected 8-week PFS of 47.5% and an acceptable lowest 8-week PFS of 23.1% in 8 weeks with a two-sided alpha error level of 0.05 and a beta error level of 0.2 using Kaplan-Meier method with Greenwood formula. We decided to recruit 38 patients to allow for a 10% dropout rate. These PFS rates were estimated with reference to the REGARD trial.10) Efficacy is assessed by Response Evaluation Criteria in Solid Tumors version 1.1.

PFS is defined as the time from the date of the first protocol treatment to the date of disease progression confirmed by computed tomography or to the date of death from any cause, whichever is shorter. ORR is defined as the proportion of patients with complete response (CR) or partial response (PR). DCR is defined as the proportion of patients with CR, PR, or stable disease. OS is defined as the time from the date of the first protocol treatment to the date of death from any cause. TTF is defined as the time from the date of the first protocol treatment to the date of treatment discontinuation for any reason. Adverse events are classified according to the Common Terminology Criteria for Adverse Events (version 4.0).

OS, PFS, and TTF are calculated by the Kaplan-Meier method. The 95% confidence intervals for 8-week PFS are calculated by the Greenwood formula. For ORR and DCR, the 95% confidence intervals are calculated by the Clopper-Pearson method.

### Study monitoring

Central monitoring is performed by the Hokkaido Gastrointestinal Cancer Study Group Data Center to ensure data submission, patient eligibility, and protocol compliance. The monitoring reports are submitted to the Hokkaido University Hospital Institute Review Board every 12 months, and safety monitoring is performed by the independent Effect Safety Committee to which all severe adverse events are reported.

### Participating institutions

The participating institutions are the Hokkaido University Hospital, Sapporo Medical Center NTT EC, Abashiri-Kosei General Hospital, Sapporo City General Hospital, Teine Keijinkai Hospital, Kushiro Rosai Hospital, Japanese Red Cross Kitami Hospital, Tomakomai Nisshou Hospital, Hakodate Municipal Hospital, Hokkaido Gastroenterology Hospital, Hakodate Central Hospital, Tomakomai City General

Hospital, Japanese Red Cross Toyama Hospital, Tonan Hospital, Sapporo Hokuyu Hospital, Iwamizawa City General Hospital, Obihiro Kosei Hospital, and Keiwakai Ebetsu Hospital.

## Conflicts of Interest

All the authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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