A Phase II Study of Systemic Chemotherapy with Docetaxel, Cisplatin, and S-1 (DCS) Followed by Surgery in Gastric Cancer Patients with Extensive Lymph Node Metastasis: Japan Clinical Oncology Group Study JCOG1002

Hiroshi Katayama1, Seiji Ito2*, Takeshi Sano3, Daisuke Takahari4, Junki Mizusawa1, Narikazu Boku5, Akira Tsuburaya6, Masanori Terashima7, Mitsuru Sasako8 and Stomach Cancer Study Group of the Japan Clinical Oncology Group

1Japan Clinical Oncology Group Data Center/Operations Office, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo, 2Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, 3GI Surgery Division, Cancer Institute Hospital, Tokyo, 4Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, 5Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, 6Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, 7Division of Gastric Surgery, Shizuoka Cancer Center, Mishima and 8Department of Surgery, Hyogo College of Medicine, Nishinomiya

*For reprints and all correspondence: Seiji Ito, Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan. E-mail: seito@aichi-cc.jp

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A Phase II trial was initiated in Japan to evaluate the efficacy and safety of preoperative chemotherapy with docetaxel, cisplatin and S-1 for gastric cancer with extensive lymph node metastasis. Patients are eligible to participate in the study if they have para-aortic lymph node metastases (stations no. 16a2/16b1) and/or a bulky lymph node (≥3 cm × 1 or ≥1.5 cm × 2) along the celiac, splenic, common or proper hepatic arteries or the superior mesenteric vein, while patients with other distant metastases are ineligible. A total of 50 patients will be enrolled over 2.5 years. The primary endpoint is the response rate of the preoperative chemotherapy, which will be assessed based on the Response Evaluation Criteria in Solid Tumors ver. 1.0. The secondary endpoints are 3-year survival, 5-year survival, proportion of patients with R0 resection, proportion of patients who complete the preoperative chemotherapy and surgery, proportion of patients who complete the protocol treatment, pathological response rate and adverse events. This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000006069.

Key words: gastric cancer – extensive lymph node metastasis – preoperative chemotherapy – Phase II

INTRODUCTION

Gastric cancer with extensive lymph node metastasis (ELM) is often unresectable. Furthermore, patients with gastric cancer and ELM often have a poor prognosis, even after an R0 resection. The Stomach Cancer Study Group of the Japan Clinical Oncology Group (SCSG/JCOG) has addressed this problem.

Since 2000, we have performed two Phase II trials (JCOG0001 and JCOG0405) to evaluate the preoperative chemotherapy followed by gastrectomy with D2 plus para-aortic lymph node dissection (PAND) for gastric cancer with ELM. In JCOG0001, the patients received two or three courses of irinotecan (70 mg/m² on days 1 and 15) and cisplatin (80 mg/m² on day 1), and then underwent surgery.
This study showed a good %3-year survival of 27.0%, but was terminated because of three treatment-related deaths (TRDs) among 55 enrolled patients (1). To develop a safer and more effective treatment, we conducted JCOG0405, in which patients received two or three courses of cisplatin (60 mg/m² on day 8) and S-1 (80 mg/m² from days 1–21) (CS) as preoperative chemotherapy and then underwent surgery. This study also showed an excellent %3-year survival of 58.8% with no TRD and low toxicity (2). Preoperative chemotherapy with CS is highly promising and is considered the current standard treatment for gastric cancer patients with ELM in SCSG/JCOG.

JCOG9501 demonstrated that prophylactic PAND did not improve survival (3). However, an integrated analysis of JCOG0001 and JCOG0405 showed a greater therapeutic index (multiplication of frequency of lymph nodes metastasis by a 3-year survival rate) (4) of para-aortic lymph node than JCOG9501 even in patients with bulky lymph node without para-aortic lymph node preoperatively (JCOG0001: 4.3, JCOG0405: 12, JCOG9501: 2.7). Therefore, we adopted the same surgical procedure as in previous studies, D2 plus PAND, for all this population.

Recently, the addition of docetaxel to cisplatin and 5-FU was shown to improve the outcome of resectable or recurrent gastric cancer patients in the USA and Europe (5). In Japan, several Phase I and Phase II trials have been conducted to evaluate a combination of docetaxel, cisplatin and S-1 (DCS) in patients with unresectable or recurrent gastric cancer (6–9). Although neutropenia and febrile neutropenia frequently occurred, the response rate was extremely high in each trial. Among several DCS regimens, we adopted the one used in the Phase II trial at Kitasato University (the Kitasato regimen) because this regimen was shown to have less toxicity and a higher response rate than other regimens. Here, we are conducting a multi-institutional Phase II trial (JCOG1002) to evaluate the efficacy and safety of DCS (the Kitasato regimen) as a preoperative chemotherapy for gastric cancer with ELM. If the efficacy and safety prove to be sufficient, we will conduct a Phase III trial to compare preoperative DCS with the current standard CS.

The JCOG Protocol Review Committee approved this study protocol in June 2011, and this study was activated in July 2011. This trial was registered at the UMIN Clinical Trials Registry (www.umin.ac.jp/ctr/) as UMIN000006069.

PROTOCOL DIGEST OF THE JCOG1002

PURPOSE

The aim of this study is to evaluate the efficacy and safety of DCS as a preoperative chemotherapy for gastric cancer with ELM.

STUDY SETTING

A multi-institutional (50 specialized centers), single-arm Phase II trial.

ENDPOINTS

The primary endpoint is the response rate to preoperative chemotherapy as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0. RECIST ver. 1.0 is used instead of ver. 1.1 because we will compare the results with previous studies using the same criteria. The secondary endpoints are %3-year survival, %5-year survival, proportion of patients with R0 resection, proportion of patients who complete the preoperative chemotherapy and surgery, proportion of patients who complete the protocol treatment, pathological response rate and adverse events.

INCLUSION CRITERIA

(i) Histologically proven primary gastric adenocarcinoma
(ii) Contrast-enhanced abdominal computed tomography (CT; 10 mm or less of slice thickness) revealed one or both of the following:
   (a) Para-aortic lymph node metastasis ≥1.0 cm between the upper margin of the celiac artery and the upper border of the inferior mesenteric artery (stations no. 16a2/16b1)
   (b) Bulky lymph nodes (≥3 cm × 1 or ≥1.5 cm × 2) along the celiac, splenic, common or proper hepatic arteries, or the superior mesenteric vein
(iii) Contrast-enhanced thoracic/abdominal/pelvic CT revealed none of the following:
   (a) Mediastinal lymph node metastasis
   (b) Lung metastasis
   (c) Peritoneal metastasis
   (d) Liver metastasis
   (e) Pleural effusion, ascites
   (f) Para-aortic lymph node metastasis other than stations no. 16a2/16b1
   (g) Other distant metastases
(iv) The macroscopic tumor type is neither the Borrmann type 4 nor large (8 cm or more) type 3
(v) No esophageal invasion or an invasion of 3 cm or less
(vi) No gastric stump cancer
(vii) No clinical signs of cervical lymph node or distant metastases
(viii) A staging laparoscopy or laparotomy performed within 28 days revealed negative washing cytology and no peritoneal metastasis
(ix) Aged between 20 and 75 years
(x) An Eastern Cooperative Oncology Group performance status of 0 or 1
(xi) No prior chemotherapy, radiotherapy or endocrine therapy for any malignancies
(xii) No prior surgery for gastric carcinoma except bypass surgery and endoscopic resection
(xiii) Fair oral intake with or without bypass surgery
(xiv) Adequate organ function
(xv) Written informed consent
EXCLUSION CRITERIA

(i) Synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma
(ii) Pregnant or breast-feeding women
(iii) Severe mental disease
(iv) Currently treated with systemic steroids
(v) HBs antigen positive
(vi) Currently treated with flucytosine, phenytoin or warfarin
(vii) Iodine allergy
(viii) History of hypersensitivity to docetaxel, cisplatin or polysorbate 80
(ix) Peripheral motor neuropathy or peripheral sensory neuropathy for any reason
(x) Edema of the limbs and trunk for any reason
(xi) Interstitial pneumonia, pulmonary fibrosis or severe emphysema
(xii) Active bacterial or fungal infections
(xiii) History of myocardial infarction or unstable angina pectoris within 6 months
(xiv) Uncontrolled hypertension
(xv) Uncontrolled diabetes mellitus or routine administration of insulin.

TREATMENT METHODS

PREOPERATIVE CHEMOTHERAPY

Patients receive an infusion of docetaxel (40 mg/m²/day) and cisplatin (60 mg/m²/day) on day 1, and take oral S-1 (80 mg/m²/day) for 2 weeks from days 1–14 followed by a 2-week rest period. Two courses of preoperative chemotherapy are administered unless unequivocal progression or unacceptable toxicities are observed. After the second course, the tumor response and feasibility of R0 resection are evaluated. When total gastrectomy with thoracotomy, left upper abdominal exenteration, pancreaticoduodenectomy or Appleby’s operation is required to achieve the R0 resection, the protocol treatment is terminated.

PREOPERATIVE EXAMINATIONS

Before enrollment, contrast enhanced thoracic/abdominal/pelvic CT (<10 mm slice thickness) and staging laparoscopy (or intra-abdominal exploration during bypass surgery) are mandatory to check the eligibility criteria. After the second or third course of preoperative chemotherapy, patients are evaluated by the following examinations to check the feasibility of the surgery:

(i) Contrast-enhanced thoracic CT
(ii) Contrast-enhanced abdominal/pelvic CT (the same slice width as baseline evaluation)
(iii) Staging laparoscopy is not mandatory

SURGERY

A total or distal gastrectomy with D2 plus PAND is performed. In the total gastrectomy for an upper gastric tumor, the spleen is also removed. Involved adjacent organ(s), if any, is also removed to achieve R0 resection. A laparoscopic gastrectomy is not allowed. If resectable M1 disease (hepatic, peritoneal and/or lymphatic metastases) is found during surgery, it is removed to achieve R0 resection. If R0 resection is impossible, the protocol treatment is terminated. When total gastrectomy with thoracotomy, left upper abdominal exenteration, pancreaticoduodenectomy or Appleby’s operation is required to achieve the R0 resection, the protocol treatment is terminated after the operation is completed.

POSTOPERATIVE CHEMOTHERAPY

After the R0 resection, adjuvant chemotherapy with S-1 is initiated within 42 days from surgery. A 6-week course consisting of 4 weeks of daily oral S-1 administration at a dose of 80 mg/m²/day followed by 2 weeks of rest is repeated during the first year after surgery. If S-1 treatment is not initiated within 12 weeks after surgery for any reason, the protocol treatment is terminated. Even after the R0 resection, if the tumor progressed during the preoperative chemotherapy and histological examination of the resected specimen showed no chemotherapeutic effect, the protocol treatment is terminated and S-1 is not administered.

FOLLOW-UP

All enrolled patients are followed for 5 years. Physical and blood examinations are conducted every 3 months for the first 3 years and every 6 months for the last 2 years. An abdominal CT is performed every 6 months for the first 3 years and every year for the last 2 years. Chest X-ray and upper gastrointestinal endoscopy are conducted every year.

STUDY DESIGN AND STATISTICAL ANALYSIS

This trial investigates the efficacy and safety of preoperative DCS followed by gastrectomy with D2 plus PAND and postoperative S-1. The primary endpoint is analyzed after the tumor response of all enrolled patients is evaluated. If this regimen proves promising, a Phase III trial will be designed to evaluate the superiority of preoperative DCS to preoperative S-1 plus cisplatin in terms of overall survival. In this Phase II trial, the sample size is 50 cases, which provides 80% power based on the hypothesis as the expected value of 80% and a threshold value of 65% in the primary endpoint using one-sided testing at a 10% significance level.
INTERIM ANALYSIS AND MONITORING

Interim analysis is not planned. The JCOG Data Center conducts data management, central monitoring and statistical analysis. If the number of TRDs reaches 3 or the number of cases with R1/R2 resection reaches 13, the registration will be suspended unless the JCOG Data and Safety Monitoring Committee approves the continuation of this trial.

PARTICIPATING INSTITUTIONS

Hakodate Goryoukaku Hospital, Iwate Medical University, National Hospital Organization, Sendai Medical Center, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Tochigi Cancer Center, National Defense Medical College, Saitama Cancer Center, National Cancer Center Hospital East, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo Metropolitan Bokutoh Hospital, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama City University Medical Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Tsubame Rosai Hospital, Toyama Prefectural Central Hospital, Ishikawa Prefectural Central Hospital, Gifu University Hospital, Gifu Municipal Hospital, Shizuoka General Hospital, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, National Hospital Organization Kyoto Medical Center, Osaka University Graduate School of Medicine, Kinki University School of Medicine, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka National Hospital, Osaka Medical College, Toyonaka Municipal Hospital, Sakai Municipal Hospital, Kansai Medical University Hirakata Hospital, Kobe University Graduate School of Medicine, Kansai Rosai Hospital, Hyogo College of Medicine, Hyogo Cancer Center, Itami City Hospital, Wakayama Medical University School of Medicine, Shimane University School of Medicine, Hiroshima City Hospital, Hiroshima City Asa Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Science Center and Oita University Faculty of Medicine.

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Conflict of interest statement

Mitsuru Sasako and Takeshi Sano state that they have received honoraria from Taiho Pharmaceutical Company for promotion of education and research in 2011.

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