A Comparison of Multimodality Treatment: Two and Four Courses of Neoadjuvant Chemotherapy Using S-1/CDDP or S-1/CDDP/Docetaxel Followed by Surgery and S-1 Adjuvant Chemotherapy for Macroscopically Resectable Serosa-positive Gastric Cancer: A Randomized Phase II Trial (COMPASS-D Trial)

Takaki Yoshikawa1*, Masataka Taguri2, Shinichi Sakuramoto3, Chikara Kunisaki4, Tetsu Fukunaga5, Seiji Ito6, Haruhiko Cho1, Kazuaki Tanabe7, Kazuhiro Nishikawa8, Takanori Matsui9, Satoshi Morita2 and Akira Tsuburaya1

1Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 2Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan, 3Department of Surgery, Kitasato University, Sagamihara, 4Department of Surgery, Yokohama City University Medical Center, Yokohama, 5Department of Gastroenterological and General Surgery, Saint Marianna University, Kawasaki, 6Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, 7Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, 8Department of Surgery, Osaka General Medical Center, Osaka and 9Department of Gastrointestinal Surgery, Aichi Cancer Center Aichi Hospital, Okazaki, Japan

*For reprints and all correspondence: Takaki Yoshikawa, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-Ku, Yokohama 241-0815, Japan. E-mail: yoshikawat@kcch.jp

INTRODUCTION

Gastric cancer is the second leading cause of cancer death in the world and is the most frequently diagnosed malignancy in Japan, South America and Eastern Europe (1). Complete resection is essential for curing gastric cancer (2). Adjuvant chemotherapy using S-1 (1 M tegafur – 0.4 M gimestat – 1 M ostat potassium) for 12 months has recently been established as the standard treatment after D2 gastrectomy in Japanese patients with Stage II or III disease (3) based on a large Phase III study (4). However, even with adjuvant S-1 chemotherapy, the prognosis for serosa-positive tumors is relatively poor.

The standard chemotherapy for metastatic disease is S-1 plus cisplatin (SC) in Japan (3), which was established from a Phase III trial (5). This trial clearly showed that SC improved the overall survival (OS) when compared with S-1 alone. Recently, the feasibility of SC was tested in an adjuvant setting to see whether this combination regimen is suitable for a test arm of a future Phase III trial (6,7). However, severe adverse events sometimes occurred during the first course of chemotherapy just after D2 gastrectomy. Thus, postoperative intensive chemotherapy may be difficult to complete.

On the other hand, preoperative (neoadjuvant) chemotherapy followed by extended surgery has some theoretical
benefits when compared with postoperative chemotherapy (8). Several Phase II studies have demonstrated that SC was safe and feasible in the neoadjuvant setting (9,10). At present, the Japan Clinical Oncology Group (JCOG) conducted a Phase III trial comparing neoadjuvant chemotherapy using two courses of SC followed by surgery and postoperative S-1 as a test arm with surgery and postoperative S-1 as a control arm for schirrhou type gastric cancer. Moreover, promising survival results were reported from a small Phase II trial evaluating two courses of SC as neoadjuvant setting for bulky nodal disease (10).

The utility of pre- and post-operative chemotherapy has been confirmed by two Phase III trials in Western countries. In a trial from the UK, three courses of pre- and post-operative chemotherapy using epirubicin, cisplatin, and 5-fluorouracil (5-FU) improved the survival compared with surgery alone (11). In a French trial, two or three courses of pre-operative chemotherapy and three or four courses of post-operative chemotherapy using 5-FU and cisplatin increased the survival compared with surgery alone (12). Therefore, suitable durations and regimens of preoperative chemotherapy have not yet been established. At present, we are testing the feasibility and efficacy of two or four courses of SC and paclitaxel plus cisplatin using a two-by-two factorial design for macroscopically resectable locally advanced gastric cancer (13). This trial, named COMPASS, was closed for recruitment in July 2011.

In the COMPASS trial, we tested doublet regimen of paclitaxel plus cisplatin which has a relatively mild toxicities than S-1 plus cisplatin (14) and is expected to have high compliance. Moreover, a total of three key drugs are sequentially used perioperatively by adding S-1 adjuvant chemotherapy. However, the response rate of paclitaxel/cisplatin was not high, 44.2% according to the previous Phase II studies (14).

Instead, a concurrent triplet regimen is attractive as the neoadjuvant chemotherapy, because a triplet regimen may have a high response rate. In fact, an S-1/cisplatin/paclitaxel combination regimen showed 63.5 and 59.1% in two Phase II trials (15,16). On the other hand, triplet regimen using docetaxel instead of paclitaxel showed much higher response rate, 87.1 and 81.3% in two Phase II studies (17,18). These results suggested that triplet regimen including docetaxel is promising in terms of response rate as the neoadjuvant chemotherapy. Docetaxel is one of key drugs used for the treatment of metastatic gastric cancer. Docetaxel has several unique characteristics, including that: (i) it is not cross-resistant with 5-FU; (ii) it is active against poorly differentiated carcinoma; (iii) it has a good transition from the blood to the peritoneal cavity; and (iv) it induces a relatively low incidence of gastrointestinal toxicities (19). The feasibility of SC plus docetaxel (SCD) has also been tested in a Phase II trial in the neoadjuvant setting for bulky nodal disease by the JCOG.

Based on these findings, we conducted a randomized Phase II trial to compare neoadjuvant chemotherapy using two and four courses of SC and SCD by a two-by-two factorial design for macroscopically resectable serosa-positive gastric cancer.

**Protocol Digest of the Study**

**Purpose**

The purpose of the study is to select the most promising cycles and regimens of neoadjuvant chemotherapy among two and four courses of SC and SCD, for a future randomized Phase III trial in patients with macroscopically resectable serosa-positive gastric cancer.

**Study Setting and Protocol Review**

The study is an open-label, randomized Phase II clinical trial. The protocol has been approved by the Protocol Review Committee of the non-profit organization Kanagawa Standard Anti-cancer Therapy Support System (KSATTS).

**Resources**

Research grants are from the KSATTS.

**Endpoints**

The primary endpoint is 3-year OS rate. The secondary endpoints are OS, progression-free survival, pathological response, clinical response, R0 resection rate, R0R1 resection rate, completion rate of the treatment, completion rate of neoadjuvant chemotherapy, incidence of adverse events and these parameters in each subset.

**Eligibility Criteria**

Tumors are staged according to the 14th edition of the Japanese Gastric Cancer Classification (20).

Inclusion criteria are as follows:

(i) Histologically proven adenocarcinoma of the stomach.

(ii) Clinical T4, or T3 disease in cases of tumors invading the esophagus and/or of the schirrhou type including giant type 3 with a maximal diameter of more than 8 cm, confirmed by abdominal computed tomography (CT) and laparoscopy. The T and N stages are determined only by CT referring to the method proposed by Habermann et al. (21). Endoscopic ultrasound is not mandatory in this trial.

(iii) No pleural effusion, no ascites exceeding pelvis and no metastasis to the peritoneum, liver or other distant organs, confirmed by abdominal—pelvic CT.

(iv) No metastasis to the lung, mediastinal lymph nodes or the other distant organs, confirmed by thoracic CT for tumors invading the esophagus.

(v) No clinically apparent distant metastasis.

(vi) Age ranging between 20 and 80.

(vii) ECOG performance status 0–1.

(viii) Enough oral intake.

(ix) No previous treatment with chemotherapy or radiation therapy for any tumors.

(x) No previous surgery for the present disease except bypass surgery.
The exclusion criteria are as follows:

(i) Remnant stomach cancer
(ii) Synchronous or metachronous cancer (synchronous multiple cancers in the stomach included)
(iii) Females with an ongoing pregnancy or breastfeeding, or who are contemplating pregnancy
(iv) Mental disorders which may affect the ability or willingness to provide informed consent or abide by the study protocol
(v) Systemic treatment with a corticosteroid
(vi) Systemic treatment with flucytosine, phenytoin or warfarin potassium
(vii) Allergic reaction to iodine
(viii) Hypersensitivity to docetaxel, cisplatin or polysorbate 80
(ix) Peripheral neuropathy
(x) Edema
(xi) Pneumonitis, lung fibrosis or emphysema in need for oxygen therapy
(xii) Active inflammation due to bacteria or fungus
(xiii) Unstable angina or cardiac infarction within 6 months
(xiv) Positive for HBs antigen or HCV antibody
(xv) Unstable hypertension
(xvi) Diabetes mellitus under treatment

REGISTRATION

The participating investigators are instructed to send an eligibility criteria report to the Data Center at the non-profit organization KSATTS. Eligible patients are registered and then randomized to one of the four groups (A, B, C and D) described in the next section by a centralized dynamic method using the following factors: schirrhous type including giant type 3 (yes/no), tumors invading the esophagus (yes/no), cT3–4a/T4b disease, lymph node metastasis (yes/no) and institution as balancing variables. Information regarding the necessary follow-up examinations and chemotherapy schedule are then sent from the Data Center. The accrual was started in October 2011 and is to continue for 3 years.

TREATMENT METHODS

The patients enrolled in this study receive one of the following neoadjuvant chemotherapy.

Group A: two courses of S-1 plus cisplatin
S-1: 80 mg/m² p.o. daily for 14 days, every 4 weeks
Cisplatin: 60 mg/m² d.i.v. day 1, every 4 weeks

Group B: four courses of S-1 plus cisplatin
S-1: 80 mg/m² p.o. daily for 21 days, every 4 weeks
Cisplatin: 60 mg/m² d.i.v. day 8, every 4 weeks

Group C: two courses of S-1 plus cisplatin plus docetaxel
S-1: 80 mg/m² p.o. daily for 14 days, every 4 weeks
Cisplatin: 60 mg/m² d.i.v. day 1, every 4 weeks
Docetaxel: 40 mg/m² d.i.v. day 1, every 4 weeks

Group D: four courses of S-1 plus cisplatin plus docetaxel
S-1: 80 mg/m² p.o. daily for 14 days, every 4 weeks
Cisplatin: 60 mg/m² d.i.v. day 1, every 4 weeks
Docetaxel: 40 mg/m² d.i.v. day 1, every 4 weeks

After completion of the neoadjuvant chemotherapy or when the tumors progress during the treatment, patients proceed to gastrectomy with standard D2 lymphadenectomy. D3 dissection or combined resection of a small part of the peritoneum or adjacent organs is permitted for curative intent, but more invasive surgeries such as pancreaticoduodenectomy or Appleby’s surgery are not. The protocol treatment is to be stopped when a curative surgery is not performed. When achieving macroscopically curative surgery, S-1 of 80 mg/m² p.o. daily for 28 days, every 6 weeks, is initiated within 6 weeks after surgery and is continued for 1 year. After completion of the protocol treatment, no other treatment is not permitted until a recurrence is detected.

STUDY DESIGN AND STATISTICAL METHODS

The present study is a randomized Phase II trial of the selection design proposed by Simon et al. (22). This study is primarily designed to evaluate (i) the effectiveness of four courses of neoadjuvant chemotherapy compared with two courses and (ii) the effectiveness of the SCD regimen compared with SC. For each purpose, the regimen showing a higher 3-year OS rate will be considered to be more promising for a subsequent Phase III trial.

The setting of COMPASS-D is very similar to JACCRO GC-01 Phase II trial (9) which is a study of neoadjuvant chemotherapy for clinically resectable T4 tumors, in terms of the target and regimen. JACCRO GC-01 showed 3-year survival rate of 43% by only one course of SC. The reference arm of COMPASS-D receives two courses of SC or SCD, or SC of two or four courses. Thus, better prognosis will be expected even in the reference arm than the result of JACCRO-GC01. Although it is difficult to assume 3-year survival rate accurately, we thought that 3-year survival rate will be around 50% in the reference arm of the COMPASS-D trial. On the other hand, triplet regimen or four courses are toxic than doublet or two courses. Considering the balance between risk and benefit, the other arm of triplet or four courses should have at least 10% increment at 3-year survival rate. Taking these into account, we assumed that the 3-year OS rate of one regimen will be 50% and that of the other regimen will be more than 60% (4). In this situation, the sample size required to ensure an at least 85% probability of the correct selection of a more effective regimen is calculated.
at 110 patients, with 55 patients per arm. Considering the occurrence of some dropouts and ineligible patients, the number of patients to be accrued is set at 120 in total.

The primary analysis in this study aims to estimate the 3-year OS rate. The OS curves are constructed as time-to-event plots by using the Kaplan–Meier method (23), and the 3-year OS and its 95% confidence interval are estimated. The 3-year OS is compared based on the normal approximation of the 3-year OS rate (z-test). Progression-free survival is also analyzed in the same manner. The pathological response, clinical response, R0 resection rate, completion rate of the treatment and completion rate of neoadjuvant chemotherapy are calculated as proportions with exact confidence intervals and then compared with Fisher’s exact test.

INTERIM ANALYSIS AND MONITORING

The Data and Safety Monitoring Committee (DSMC) independently review the report of trial monitoring regarding the efficacy and safety data from the present study. Based on the monitoring, the DSMC can consider early termination of a treatment regimen if non-hematological toxicities of Grade 3 or more are present in more than 20% of patients or if the number of patients with febrile neutropenia of Grade 4 exceeds 10% when the enrollment exceeds 20 patients. Protocol compliance, safety and on-schedule study progress are also monitored by the DSMC.

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Conflict of interest statement

None declared.

References