Table 2 Treatments provided

Gastrectomy	82
Total gastrectomy	55
Distal gastrectomy	27
Chemotherapy	121
5-FU	8
S1	43
S1/CDDP	27
MTX/5-FU	28
CPT11/CDDP	5
Others	10
Number of regimens administered	
1st line	44
2nd line	35
3rd line	24
4th line	16
5th line	1
6th line	1

FU fluorouracil, *CDDP* cisplatin, *MTX* methotrexate, CPT11 irinotecan

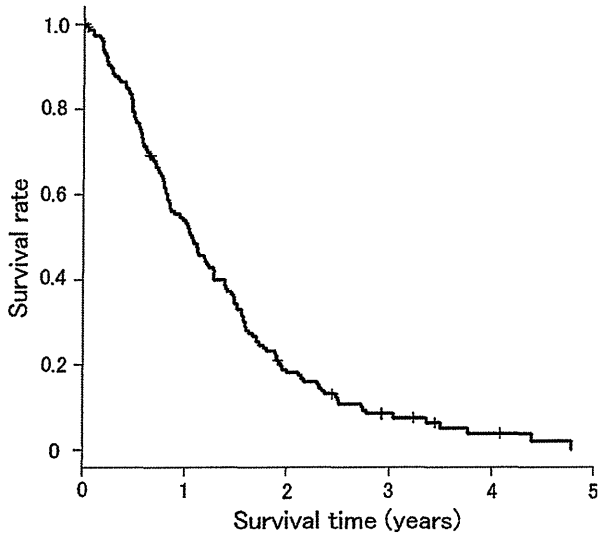

Fig. 1 Survival curves of patients included in this study. MST is 390 days. One- and three-year survival rates are 53.9 and 18.1 %, respectively

Investigation of 40 patients with localized peritoneal metastasis (P1)

The degree of peritoneal metastasis was confirmed by laparotomy in 106 of the 148 patients: it was P1 in 40 patients, P2 in 12 patients, and P3 in 54 patients. Survival analysis was conducted in 40 patients with P1 peritoneal metastasis. R0 resection according to 6th edition of the TNM classification was performed in 18 patients and the MST for these patients (26.4 months) was longer than that of the 16 patients who underwent R1 or R2 gastrectomy (Fig. 3, 12.3 months; $P < 0.001$) [27].

Discussion

Recent advances in chemotherapy regimens have improved the survival rates of gastric cancer patients with incurable factors. Koizumi et al. [5] reported an MST of 13 months in patients with advanced gastric cancer who were treated with S1 and cisplatin, and Bang et al. [6] reported a 13.8 month median overall survival time in patients with HER2-positive advanced gastric cancer who were treated with trastuzumab plus chemotherapy. However, to date, the effects of chemotherapy are limited and the 5 year survival rate of patients with unresectable gastric cancer remains grim [5, 6].

The feasibility of palliative gastrectomy in patients with unresectable gastric cancer is under debate [14, 18–24]. Many studies have examined a variety of patients with gastric cancer; however, the type and the number of incurable factors differed among patients. To the best of our knowledge, the present study is the first report that investigates a similar group of patients who all had peritoneal metastasis but did not have other obvious incurable factors. Therefore, we were able to identify the appropriate treatment strategy for patients with peritoneal metastasis with less bias than the previous studies.

The present study showed that there was no survival benefit associated with palliative gastrectomy. Instead, we recommend chemotherapy, as long as patients do not have tumor-associated symptoms. Sarela et al. [13, 14], and Kahlke et al. [20] also did not recommend palliative gastrectomy if patients did not have tumor-associated symptoms because it did not affect the patient's survival time. In contrast, Kim et al. [19] and Li et al. [23] recommended palliative gastrectomy, and Lin et al. [28] recommended palliative gastrectomy with subsequent chemotherapy to improve the survival rate of patients.

Multivariate analysis identified pretreatment ECOG performance status, macroscopic tumor type, and chemotherapy as independent prognostic factors. Macroscopic tumor type 4 is a widely accepted prognostic factor, and the incidence of peritoneal metastasis associated with type 4 tumors is higher than with other macroscopic tumor types [3, 4, 22]. Poor ECOG performance status is also a well-known independent prognostic factor in advanced malignancies [13, 16, 20]. Sarela et al. [13] reported that poor ECOG performance status is an independent prognostic factor in patients with peritoneal metastasis, as found in our study.

We also investigated the efficacy of R0 surgery in patients with localized peritoneal metastasis and found that

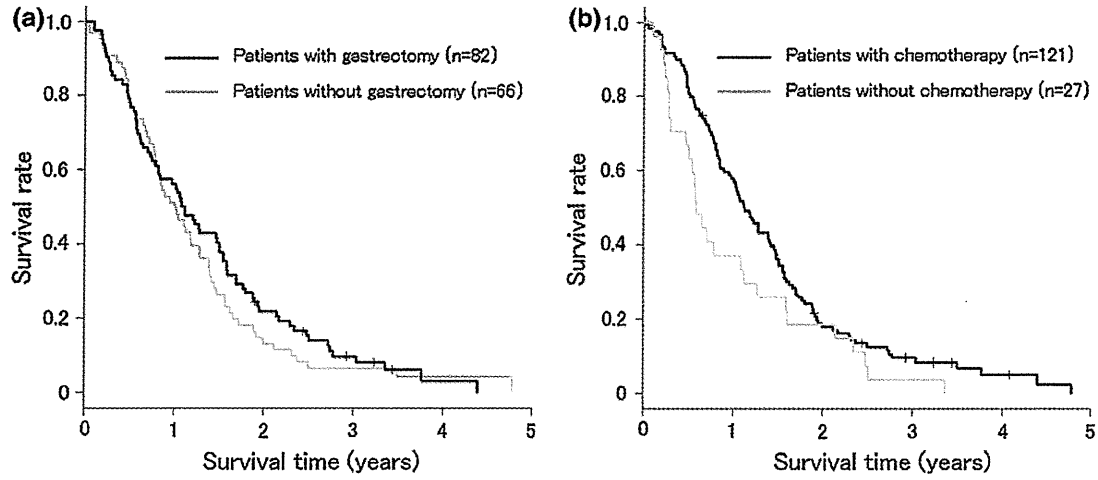

Fig. 2 **a** Survival curves of patients with or without gastrectomy. There is no difference in MST between patients with gastrectomy (13.1 months; $n = 82$) and those without gastrectomy (12.0 months; $n = 66$; $P = 0.410$). **b** Survival curves of patients who received or did not receive chemotherapy. MST was significantly longer for patients who received chemotherapy (13.7 months; $n = 121$) than for those who did not (7.1 months; $n = 27$; $P = 0.048$)

Table 3 Results of multivariate analysis

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (<60 years vs. ≥60 years)	0.830	1.045	0.700–1.559
Sex (male vs. female)	0.516	0.879	0.596–1.297
cP (cP− vs. cP+)	0.122	0.681	0.419–1.108
Gastrectomy (yes vs. no)	0.897	1.031	0.646–1.647
Chemotherapy (yes vs. no)	0.004	0.476	0.288–0.787
ECOG performance status (0,1 vs. 2,3)	<0.001	0.278	0.156–0.495
Macroscopic type (≠type 4 vs. type 4)	0.006	0.566	0.377–0.848
Histology (differentiated vs. undifferentiated)	0.290	0.466	0.454–1.256

ECOG Eastern Cooperative Oncology Group

the survival rate was better in patients who were able to undergo curative resection than those who were not. Ouchi et al. [18] segregated patients according to the degree of peritoneal metastasis (P1 vs. P2 or P3) because they believed that the tumor load must also be taken into account. Moreover, Hioki et al. [29] reported a better outcome in patients with localized peritoneal metastasis following gastrectomy than in those with widespread peritoneal metastasis, and emphasized that patients with a good performance status and localized peritoneal metastasis should be considered appropriate surgical candidates. Based on the results from these reports it may be plausible to distinguish whether patients have localized or widespread peritoneal metastases in order to establish the appropriate treatment strategy for these patients.

However, it has been reported that the accuracy of computed tomography for diagnosing peritoneal metastasis is limited, and the degree of peritoneal metastasis would not be diagnosed without laparotomy [30]. Recently, the feasibility of diagnostic laparoscopy, which is less invasive than laparotomy and more sensitive for finding peritoneal metastasis than computed tomography, was reported [31, 32]. In our institute, we also perform this procedure in patients in whom a high incidence of peritoneal metastasis was estimated. However, we began diagnostic laparoscopy in the middle of 2008 so most of the patients in the present series did not receive diagnostic laparoscopy before treatment.

There are limitations associated with this retrospective study. These include a possible bias in the selection of treatment strategies, including chemotherapeutic regimens and indication for gastrectomy, and the possibility that patient backgrounds differ between groups. In fact, patient age and the incidence of clinically evident peritoneal metastasis were different between groups. Therefore, we conducted multivariate analysis including these factors as covariates. To overcome these problems and to obtain conclusive results, a well-designed prospective trial is necessary. Groups in Japan and Korea are currently collaborating on an international randomized controlled trial

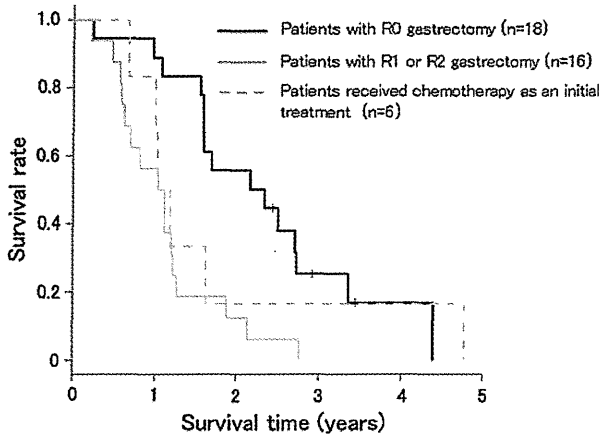

Fig. 3 Survival curves of 40 patients with localized peritoneal metastasis confirmed by laparotomy. MST was significantly longer in 18 patients who underwent R0 gastrectomy (26.4 months) than in 16 patients who underwent R1 or R2 gastrectomy (12.3 months; $P < 0.001$). MST for 18 patients with R0 gastrectomy was also longer than that for six patients who received chemotherapy as an initial treatment (12.5 months), although this was not statistically significant ($P = 0.414$)

investigating the efficacy of gastrectomy in gastric cancer patients with a single incurable factor. Therefore, we must await the results of this study, although the patients being investigated in the prospective study are not identical to those included in the present study [33].

In the present study, we used overall survival to evaluate the efficacy of each treatment. We could not evaluate patient quality of life after treatment, the burden of care, and cost because it was difficult to collect these data retrospectively. However, these factors should also be taken into account, particularly in patients with incurable disease [34]. If poor quality of life and increased burden of care were observed in patients who had undergone gastrectomy, they would further reinforce the arguments against gastrectomy in patients having peritoneal metastasis.

In conclusion, the results of the present study did not show a survival benefit with palliative gastrectomy in patients with peritoneal metastasis. Instead, chemotherapy has to be considered an initial treatment for these patients. We still have to await the result of randomized controlled trial being performed in the East to address this specific issue.

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JJCO Japanese Journal of Clinical Oncology

Clinical Trial Note

Jpn J Clin Oncol 2012;42(6)556–559
doi:10.1093/jjco/hys054
Advance Access Publication 23 April 2012

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

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Received December 27, 2011; accepted March 16, 2012

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 ($\geq$3 cm $\times$ 1 or $\geq$1.5 cm $\times$ 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/m^2 on days 1 and 15) and cisplatin (80 mg/m^2 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/m^2 on day 8) and S-1 (80 mg/m^2 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 unresectable 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 $\geq$1.0 cm between the upper margin of the celiac artery and the upper border of the inferior mesenteric artery (stations no. 16a2/16b1)
  (b) Bulky lymph nodes ($\geq$3 cm $\times$ 1 or $\geq$1.5 cm $\times$ 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/m^2/day) and cisplatin (60 mg/m^2/day) on day 1, and take oral S-1 (80 mg/m^2/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 possible, the patient undergoes surgery within 56 days (preferably 28 days) after the last S-1 treatment. When R0 resection is considered difficult despite tumor shrinkage after the second course, the patient receives the third course of DCS before surgery.

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
(iv) Tumor marker (CEA, CA19-9)
(v) Adequate organ function.

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/m^2/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 Prefectual 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.

Funding

This study is supported by the National Cancer Center Research and Development Fund (23-A-16, 23-A-19) and the Health and Labour Sciences Research Grant for Clinical Cancer Research (H22-Gan-016) from the Ministry of Health, Labour and Welfare of Japan.

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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Cancer Chemother Pharmacol (2012) 69:949–955
DOI 10.1007/s00280-011-1783-9

ORIGINAL ARTICLE

Pharmacokinetic analysis of capecitabine and cisplatin in combination with trastuzumab in Japanese patients with advanced HER2-positive gastric cancer

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Received: 22 April 2011 / Accepted: 8 November 2011 / Published online: 25 November 2011

Abstract
Purpose To evaluate the pharmacokinetics (PK) of capecitabine and cisplatin, administered in combination with or without trastuzumab, in Japanese patients with HER2-positive advanced gastric cancer (AGC).
Methods Patients eligible for this PK study (study JP19959), which was carried out during treatment Cycle 1 of the ToGA study, received either capecitabine and cisplatin (XP arm) or trastuzumab plus capecitabine and cisplatin (HXP arm). All patients received capecitabine (1,000 mg/m^2 orally, twice daily for 14 days) and cisplatin (80 mg/m^2 intravenous infusion on Day 1). Patients in the HXP arm also received trastuzumab (8 mg/kg intravenous infusion on Day 1), concurrently with capecitabine. No further study medication was administered during study JP19959. Serial plasma samples for PK analysis were obtained at intervals before and after the administration of capecitabine and cisplatin on Day 1.
Results Twenty-two patients were enrolled in this PK study: eight in the HXP arm and 14 in the XP arm. All blood samples were available for PK analysis. Co-administration of trastuzumab resulted in no statistically or clinically significant changes in the PK profiles of capecitabine or its metabolites, or of cisplatin (total or unbound platinum).
Conclusions Variability in the AUC_{last} and C_{max} values for the capecitabine was consistent with the known PK profile of capecitabine and fell within established limits. Concurrent trastuzumab therapy is unlikely to alter the PK or safety profile of capecitabine or cisplatin in Japanese patients with HER2-positive AGC.

Keywords Capecitabine · Cisplatin · Trastuzumab · ToGA study · Pharmacokinetics · Advanced gastric cancer

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Introduction

Gastric cancer is one of the most frequent causes of cancer-related deaths, and chemotherapy is the standard treatment for advanced disease. In Europe, the combination of epirubicin, cisplatin, and 5-fluorouracil (5-FU) (ECF) is widely accepted as the standard chemotherapy regimen on the basis of the results from studies in patients with advanced esophagogastric cancer [1, 2]. In contrast, in the

United States, combinations of docetaxel, cisplatin, and 5-FU (DCF), including modified DCF regimens, are generally used as reference regimens [3, 4]. In Japan, Korea, and China, S-1 (a new oral antitumor agent that consists of tegafur, 5-chloro-2,4-dihydroxypyridine, and oxonic acid) is also available for the treatment of gastric cancer. Thus, there is no global standard regimen for the first-line treatment of advanced gastric cancer (AGC). Regimens combining 5-FU and cisplatin (FP) are, however, commonly used in routine clinical practice in many countries for the first-line treatment of AGC [5–7].

Capecitabine (Xeloda, F. Hoffmann-La Roche) is an oral fluoropyrimidine and a prodrug for 5-FU, which is designed to mimic a continuous infusion of 5-FU and enhance activity in tumor tissues. It is currently approved globally for the treatment of metastatic breast cancer, adjuvant colon cancer, metastatic colorectal cancer, metastatic pancreatic cancer, and AGC. Capecitabine can replace infused 5-FU in triplet combinations for the treatment of AGC [8]. A regimen combining capecitabine and cisplatin (XP) was shown to be an effective and well-tolerated therapy for the first-line treatment of AGC in the ML17032 trial [9].

Trastuzumab (Herceptin, Genentech) is a humanized monoclonal antibody that binds to human epidermal growth factor receptor 2 (HER2), resulting in anticancer effects. In the Trastuzumab for GAstric cancer (ToGA) phase III international study, trastuzumab in combination with chemotherapy demonstrated a significant and clinically relevant survival benefit in patients with HER2-positive AGC, without new or unexpected side effects [10]. In October 2010, the United States Food and Drug Administration (FDA) approved Trastuzumab in combination with cisplatin and capecitabine, for the treatment of patients with HER2-positive metastatic gastric cancer. A regimen combining trastuzumab, capecitabine, and cisplatin is, therefore, a new therapeutic option for patients with HER2-positive AGC.

There is evidence to suggest that, although the pharmacokinetic (PK) interactions between capecitabine and cisplatin lead to the accumulation over time when the two agents are co-administered, this PK interaction does not lead to a negative pharmacodynamic effect (i.e., increased toxicity) [11]. Furthermore, a study in patients with inoperable esophagogastric carcinoma has demonstrated that the PK profile of capecitabine is not significantly influenced when this drug is co-administered with epirubicin and cisplatin [12]. However, it is not known whether the PK profiles of capecitabine and cisplatin are affected by concomitant administration of trastuzumab in patients with AGC.

The PK profile of capecitabine, administered as a component of combination chemotherapy, has not previously been studied in Japanese patients with gastric cancer. While previous studies suggest that race does not influence the PK profile of capecitabine administered as monotherapy [13–15], we conducted a study to evaluate the PK profiles of capecitabine and cisplatin administered in combination with or without trastuzumab in patients enrolled into the ToGA study at Japanese centers.

Patients and methods

Patient characteristics

This Japanese pharmacokinetic study (JP19959) was a substudy of the ToGA study (BO18255; NCT01041404). Patients enrolled in the ToGA study had inoperable locally advanced or recurrent and/or metastatic adenocarcinoma of the stomach or gastro-esophageal junction, had HER2-positive tumors, and had not received any previous treatment for their advanced/metastatic disease. Additional eligibility criteria of the ToGA study were as follows: age $\geq$18 years; Eastern Cooperative Oncology Group (ECOG) performance status $\leq$2; no adjuvant chemotherapy within 6 months; no radiotherapy or major surgery within 4 weeks; no investigational anti-cancer therapy within 4 weeks; adequate end-organ function and renal function; baseline left ventricular ejection fraction (LVEF) >50%; measurable or evaluable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST); and a life expectancy $\geq$3 months. All patients gave written informed consent to participate in the ToGA study and in this substudy. The protocol and consent were reviewed and approved by the institutional review boards at each participating institution.

Treatment

All treatments (trastuzumab, capecitabine, and cisplatin) were included in the ToGA study. Patients eligible to participate in this substudy received capecitabine and cisplatin during treatment Cycle 1 of the ToGA study. While patients randomized to the XP arm received no additional therapy, patients randomized to the trastuzumab plus XP (HXP) arm received trastuzumab. No further study medication was administered during the ToGA study.

All patients in the JP19959 study received capecitabine (1,000 mg/m^2 orally) twice daily for 14 days, beginning on the morning of Day 1 of Cycle 1. Patients randomized to the HXP arm received a concurrent intravenous infusion of trastuzumab (8 mg/kg loading dose over 90 min on Day 1; subsequent doses: 6 mg/kg). Cisplatin was administered at the same dose in both treatment groups (80 mg/kg via intravenous infusion over 2 h on Day 1), beginning 2.0–2.5 h after administration of capecitabine. Thus, in the

HXP arm, 30–60 min elapsed between completion of the trastuzumab infusion and initiation of dosing with cisplatin.

Plasma sampling and drug assay

Blood samples (5 mL) for the measurement of capecitabine and its metabolites were collected at the following time points on Day 1 of Cycle 1: before administration of capecitabine; 1, 2, 3, and 8–12 h after administration of capecitabine; at the end of cisplatin infusion; and 2 h after the end of cisplatin infusion. These blood samples were collected into sampling tubes containing Na-EDTA, gently inverted several times to mix thoroughly, and immediately centrifuged at 1,500×*g* for 10 min at 4°C. The supernatant plasma was then placed in a designated tube and stored frozen at −20°C or colder until shipping to Covance Laboratories (WI, USA) for analysis. The concentrations of capecitabine and its metabolites (5′-deoxy-5-fluorocytidine [5′-DFCR], 5′-deoxy-5-fluorouridine [5′-DFUR], 5-FU, and α-fluoro-β-alanine [FBAL]) in plasma were determined using liquid chromatography tandem mass spectrometry (LC/MS–MS) [16].

Blood samples (5 mL) for the measurement of cisplatin PK were obtained at the following times on Day 1 of Cycle 1: before the cisplatin infusion; at the end of the cisplatin infusion; 1 and 2 h after the end of the infusion; and 8–12 h after administration of capecitabine. These blood samples were collected into sampling tubes containing heparin, gently inverted several times to mix thoroughly, and immediately centrifuged at 1,500×*g* for 10 min at 4°C. An aliquot (500 μL) of the obtained plasma was stored in a designated tube as a sample for total platinum concentration measurement, while the remaining plasma was dispensed into 4 designated centrifuge filter tubes (in portions of approximately 400 μL plasma) for ultrafiltration, and centrifuged at 1,500×*g* (not exceeding 2,000×*g*) for 30 min at 4°C. The obtained ultrafiltered plasma was placed in designated tubes as samples for measurement of unbound platinum concentration. All the samples for cisplatin measurements were stored frozen at −20°C or colder until shipping to Advion BioSciences (NY, USA) for the analysis. Total platinum and unbound platinum concentrations were measured by inductively coupled plasma mass spectrometry (ICP-MS).

Pharmacokinetic analyses

The PK parameter values for capecitabine (both prodrug and metabolites) and cisplatin (total platinum in plasma and unbound platinum in ultrafiltered plasma) were calculated with WinNonlin (Version 4.01, Pharsight, CA, USA) using non-compartmental models. For capecitabine and its metabolites, extravascular input (model 200) was used. For cisplatin constant infusion, model 202 was used. The PK parameter values calculated for capecitabine and its metabolites in plasma, and for total platinum in plasma and unbound platinum in ultrafiltered plasma for cisplatin, were the maximum plasma concentration (C_{max}), the time of maximum plasma concentration (T_{max}), the area under the plasma concentration–time curve (AUC) for time zero to infinity (AUC_{inf}), the AUC for time zero to last measured time (AUC_{last}), the elimination rate constant (K_{el}), the elimination half-life ($t_{½}$), clearance (CL), the apparent total clearance (CL/*F*), and the volume of distribution at steady state (V_{ss}). For each parameter, means and standard deviations (SD) of values for the 2 treatments were calculated. For between-group comparison, AUC_{last} values were natural-logarithmically transformed and the ratio and 90% confidence intervals (CI) for the XP arm were compared with those of the HXP arm.

The PK parameter values for capecitabine and its metabolites obtained in this study were compared with the PK parameter values for capecitabine obtained in a Japanese study of capecitabine monotherapy in gastric cancer [17] and with the published PK profile of capecitabine [13–15, 18]. It has previously been reported that the PK profile of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU, and FBAL) shows dose proportionality [13–15, 18]. The C_{max}, AUC_{last}, and AUC_{inf} values in the present study were, therefore, dependant on the dose of capecitabine. Statistical analysis were performed to test the difference of AUC_{last} values for capecitabine, 5-FU and FBAL among XP, HXP and X only group using Welch's test by TIBCO Spotfire S+ (Version 8.1 J,TIBCO Software Inc., CA, USA). Similarly, the PK parameter values for cisplatin were compared with those found in previous publications [19–22].

Results

Patient characteristics

A total of 22 patients from seven institutions in Japan were enrolled into this substudy between June 2006 and January 2008: eight patients were enrolled into the XP arm and 14 patients into the HXP arm, and all were evaluable for PK. The patient characteristics were similar in the two treatment groups (Table 1).

Effect of trastuzumab and cisplatin on the pharmacokinetics of capecitabine

The PK parameter values obtained for capecitabine and its metabolites are summarized in Table 2. Following the administration of capecitabine, the mean T_{max} for

Table 1 Patient characteristics (mean ± SD)

Characteristic	XP arm	HXP arm
Number of patients (male/female)	8 (3/5)	14 (2/12)
Gastrectomy (yes/no)	2/6	0/14
Liver function (normal/mild-to-moderate dysfunction)	5/3	5/9
Weight (kg)	53.9 ± 13.7	54.1 ± 9.3
Height (cm)	160 ± 16.2	163 ± 7.5
Creatinine clearance (mL/min)	85.7 ± 22.2	86.4 ± 24.0
Body surface area (m^2)	1.55 ± 0.28	1.57 ± 0.16

capecitabine, 5′-DFCR (intermediate metabolite), 5′-DFUR, and 5-FU (metabolites with antitumor activity) was obtained between 1.36 and 1.62 h in the XP arm and between 1.98 and 2.20 h in the HXP arm. The mean C_{max} of FBAL (the main catabolite of 5-FU) was reached after 2.72 h in XP the arm and after 3.04 h in the HXP arm. The mean C_{max} for capecitabine was numerically greater in the HXP arm (4.60 ± 5.46 μg/mL) than in the XP arm (2.21 ± 0.85 μg/mL). Similarly, the AUC_{last} value for capecitabine was larger in the HXP arm (6.56 ± 5.63 μg h/mL) than in the XP arm (3.65 ± 1.42 μg h/mL). However, the expected variation in C_{max} and AUC_{last} values observed between treatment arms was not clinically significant and fell within established ranges. The C_{max} of FBAL was reached slightly later than the other metabolites and decreased slowly in both arms. The $t_{½}$ of FBAL was correspondingly longer than that of capecitabine or other metabolites: 2.07 h in the XP arm and 2.41 h in the HXP arm. Conversely, capecitabine, 5′-DFCR, 5′-DFUR, and 5-FU were all rapidly eliminated in both arms: the mean $t_{½}$ of capecitabine and its metabolites ranged from 0.44 to 0.74 h in the XP arm and from 0.87 to 0.93 h in the HXP arm.

Effect of trastuzumab and capecitabine on the pharmacokinetics of cisplatin

The PK parameter values obtained for cisplatin are summarized in Table 3. The mean C_{max} values for total platinum were 4.00 μg/mL in the XP arm and 3.70 μg/mL in the HXP arm, with mean $t_{½}$ values of 13.9 h and 17.9 h, respectively. For unbound platinum, the mean C_{max} values were 1.83 μg/mL in the XP arm and 1.97 μg/mL in the HXP arm, with mean $t_{½}$ values of 1.28 and 1.11 h, respectively. There was no difference between the 2 treatment arms in the PK for total platinum or for unbound platinum. The ratios (HXP arm/XP arm) of $\ln(AUC_{last})$ for total and unbound platinum are shown in Fig. 1. The 90% CI of these ratios included 100%, indicating that there was

Table 2 Pharmacokinetic parameters for capecitabine and its metabolites (mean ± SD)

Group	Compound	*N*	T_{max} (h)	C_{max} (μg/mL)	AUC_{last} (μg h/mL)	AUC^{a}_{inf} (μg h/mL)	$t^{a}_{½}$(h)	CL/F^{a} (L/h)
XP	Capecitabine	8	1.36 ± 0.75	2.21 ± 0.85	3.65 ± 1.42	3.65 ± 1.54[b]	0.44 ± 0.12[b]	252 ± 141[b]
	5′-DFCR	8	1.48 ± 0.76	5.03 ± 2.00	10.3 ± 1.86	10.3 ± 1.85	0.69 ± 0.12	52.5 ± 12.0
	5′-DFUR	8	1.62 ± 0.75	4.81 ± 2.74	8.34 ± 2.19	8.72 ± 2.17[c]	0.74 ± 0.42[c]	61.6 ± 20.1[c]
	5-FU	8	1.61 ± 0.92	0.19 ± 0.14	0.32 ± 0.14	0.36 ± 0.14[c]	0.73 ± 0.38[c]	924 ± 569[c]
	FBAL	8	2.72 ± 0.69	3.80 ± 0.85	15.1 ± 5.14	16.9 ± 6.61[b]	2.07 ± 0.52[b]	14.9 ± 5.14[b]
HXP	Capecitabine	14	1.98 ± 0.91	4.60 ± 5.46	6.56 ± 5.63	7.88 ± 6.48[d]	0.89 ± 0.47[d]	148 ± 83.0[d]
	5′-DFCR	14	2.05 ± 0.87	5.08 ± 2.70	12.0 ± 5.58	11.9 ± 5.72[e]	0.93 ± 0.32[e]	54.1 ± 28.1[e]
	5′-DFUR	14	2.12 ± 0.90	3.45 ± 1.73	7.60 ± 2.25	7.76 ± 2.17[f]	0.87 ± 0.36[f]	76.5 ± 39.8[f]
	5-FU	14	2.20 ± 0.84	0.15 ± 0.10	0.36 ± 0.12	0.33 ± 0.14[f]	0.88 ± 0.39[f]	972 ± 523[f]
	FBAL	14	3.04 ± 0.96	3.55 ± 1.02	13.9 ± 3.84	17.2 ± 5.02[f]	2.41 ± 0.59[f]	14.6 ± 5.06[f]

[a] Some samples were not able to calculate K_{el} by lack of data in the elimination phase, [b] $N = 7$, [c] $N = 6$, [d] $N = 9$, [e] $N = 13$, [f] $N = 10$

Table 3 Pharmacokinetic parameters for cisplatin (mean ± SD)

Group	Parameter	*N*	C_{max} (μg/mL)	AUC_{last} (μg h/mL)	AUC^{a}_{inf} (μg h/mL)	$t^{a}_{½}$ (h)	CL^{a} (L/h)	V^{a}_{ss} (L)
XP	Total platinum	8	4.00 ± 0.51	14.8 ± 2.20	60.1 ± 13.4[b]	13.9 ± 4.84[b]	2.26 ± 0.65[b]	41.5 ± 10.7[b]
	Unbound platinum	8	1.83 ± 0.30	3.46 ± 0.52	3.58 ± 0.52	1.28 ± 0.38	35.6 ± 9.52	55.1 ± 16.2
HXP	Total platinum	14	3.70 ± 0.89	13.4 ± 2.95	71.1 ± 91.2[c]	17.9 ± 23.9[c]	2.89 ± 1.39[c]	43.0 ± 4.53[c]
	Unbound platinum	14	1.97 ± 0.65	3.64 ± 1.11	3.79 ± 1.15[d]	1.11 ± 0.18[d]	35.3 ± 14.3[d]	52.2 ± 23.9[d]

[a] Some samples were not able to calculate K_{el} by lack of data in the elimination phase, [b] $N = 7$, [c] $N = 12$, [d] $N = 13$

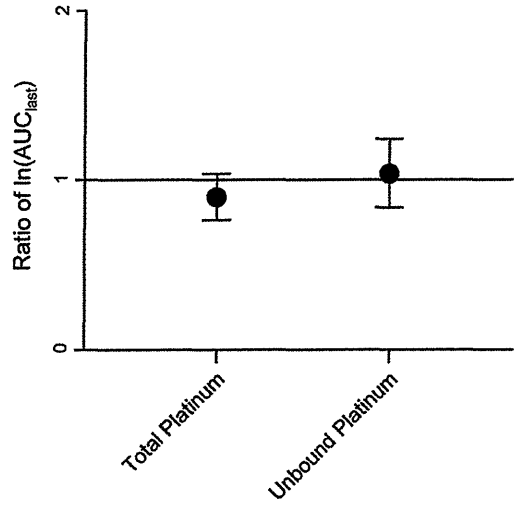

Fig. 1 The ratios (HXP arm/XP arm) of ln(AUC_{last}) for total and unbound platinum. *Error bars*, 90% CI

no clear difference in exposure to cisplatin between the XP and HXP arms.

Pharmacokinetics of capecitabine and cisplatin: comparison with the literature

Dose-normalized AUC_{last} values for capecitabine, 5-FU, and FBAL are displayed in Fig. 2. High interpatient variability in the PK profile of capecitabine is well documented. Consequently, limits of variability for AUC and C_{max} values for capecitabine treatment regimens have been defined and reported [16, 23, 24]. Briefly, for AUC values, acceptable between-treatment differences in 90% CIs fall within the range of 80 to 125%, whereas for C_{max} values, acceptable variability falls within the range of 70–143%. In this analysis, the 90% CIs for ratios of C_{max} and AUC_{last} values for capecitabine, with or without trastuzumab, fell within previously reported limits, indicating that there were no remarkable changes in the PK profile of capecitabine when co-administered with trastuzumab. Furthermore, the means and ranges of distribution of capecitabine metabolites were consistent, irrespective of whether capecitabine was administered alone (*X* only), with cisplatin (XP), or with trastuzumab and cisplatin (HXP). No significant differences of AUC_{last} values for capecitabine, 5-FU and FBAL among XP, HXP and *X* only group were observed.

After intravenous administration, cisplatin is rapidly and irreversibly bound to plasma proteins, and only the unbound fraction remains biologically active [19]. We therefore compared the PK parameter values obtained for unbound platinum in this study with those obtained in previously published studies (Table 4). In non-small-cell lung cancer patients who were treated with 80 mg/m^2 cisplatin, the mean unbound platinum C_{max} was 3.08 μg/mL and the mean AUC value was 2.0 μg h/mL [20]. Felici et al. [19] reported that, in patients with solid tumors treated with 75 mg/m^2 cisplatin, C_{max} was 1.22 and 1.18 μg/mL, and the value for AUC_{inf} was 3.72 and 3.67 μg h/mL for the docetaxel + cisplatin and docetaxel + cisplatin + 5-FU arms, respectively. Thus, the mean C_{max} values obtained in this study (1.83 μg/mL for the XP arm and 1.97 μg/mL for the HXP arm; Table 3) are similar to those previously reported, as are the AUC_{inf} values (3.58 μg·h/mL for the XP arm and 3.79 μg h/mL for the HXP arm; Table 3). In previous studies, Urien et al. [21] and Hanada et al. [22] reported that the mean CL values for unbound platinum were 35.5 and 18.5 L/h, respectively. The CL values from this study (35.6 and 35.3 L/h for the XP and HXP arm, respectively; Table 3) are, therefore, also consistent with previously reported data.

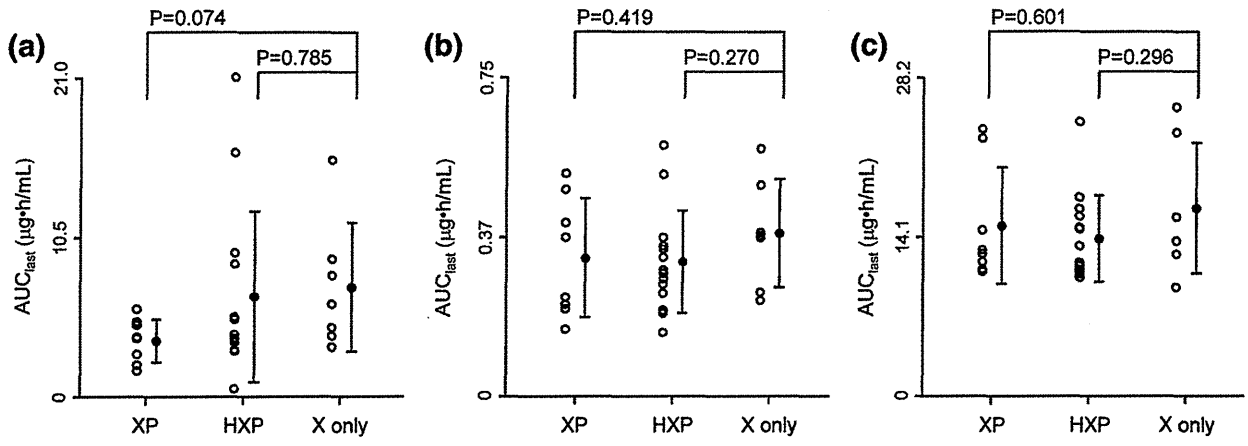

Fig. 2 Dose-normalized AUC_{last} for **a** capecitabine, **b** 5-FU, and **c** FBAL. Mean ± SD. *X*, capecitabine; *P*, cisplatin; *H*, trastuzumab. *P* values were calculated by Welch's test

Table 4 Comparison of pharmacokinetic parameters of unbound platinum (mean ± SD or mean)

	JP19959 (current study)		Previous data				
	XP	HXP	Felici et al. [19]		Kitajima et al. [20]	Urien et al. [21]	Hanada et al. [22]
			TC	TCF			
Cisplatin (mg/m^2)	80	80	75	75	80	15–80	60–100
AUC_{inf} (μg h/mL)	3.58 ± 0.52	3.79 ± 1.15	3.72	3.67	2.0	–	–
C_{max} (μg/mL)	1.83 ± 0.30	1.97 ± 0.65	1.22	1.18	3.08	–	–
CL (L/h)	35.6 ± 9.52	35.3 ± 14.3	39.2	39.9	–	35.5	18.5

T docetaxel, *C* cisplatin, *F* 5-fluorouracil

Discussion

Several chemotherapeutic agents are considered to be active in AGC. These include 5-FU, cisplatin, anthracyclines, oral fluoropyrimidines, intravenous fluoropyrimidines, irinotecan, oxaliplatin, and docetaxel. Although regimens containing 5-FU and cisplatin are widely accepted as potential standard therapies for advanced gastric and esophagogastric cancer, they are associated with response rates of 25–45% and a median overall survival time limited approximately 7–9 months [1–4]. Thus, there is a requirement for more efficacious treatments.

The efficacy and safety findings of the pivotal ToGA study have been reported [10]. Briefly, addition of trastuzumab to chemotherapy extended the median overall survival time of patients with HER2-positive AGC by 2.7 months compared with chemotherapy alone (hazard ratio 0.74, 95% CI: 0.60–0.91; $P < 0.005$). In patients limited to those with highly HER2-positive tumors (graded as immunohistochemistry [IHC] 2+/fluorescence *in situ* hybridization [FISH]-positive or IHC 3+), median overall survival was 16.0 months for patients receiving trastuzumab plus chemotherapy compared with 11.8 months for chemotherapy alone. Importantly, the overall treatment safety profiles of the 2 study arms were similar, indicating that the addition of trastuzumab did not adversely affect treatment safety [10].

The testing of any new combination of molecular-targeted agents must take into account drug–drug interactions that may negatively affect treatment-related adverse events. The primary analyses performed in the ToGA study focused on comparing treatment efficacy and safety, and included data obtained from 584 patients. The population of the ToGA study was broad and heterogeneous, enrolling patients from all over the world, with over 50% of the patients enrolled from Asian regions. The aim of the present study was to characterize the PK profiles of capecitabine and cisplatin when given in combination with trastuzumab in Japanese patients with HER2-positive AGC, and to identify any major drug–drug interactions. The data presented here are obtained from Japanese patients who were enrolled into the ToGA study and who agreed to participate in a PK-monitoring substudy.

The results of the present study show that the addition of trastuzumab to chemotherapy (XP) does not result in any consistent or clinically significant changes in the PK profile of either capecitabine (prodrug or metabolites) or cisplatin (total or unbound platinum) when administered concurrently in Japanese patients with HER2-positive AGC. This finding, coupled with safety profiles in ToGA study, suggests that drug–drug interactions are unlikely to occur.

Moderate variability in the PK profile of the capecitabine was observed between treatment arms, but this was not surprising because orally administered cytotoxic drugs (such as capecitabine) are slowly absorbed and extensively metabolized, resulting in high interpatient variability in exposure [24]. Furthermore, variations in AUC_{last} and C_{max} values for capecitabine were comparable with those observed in previous PK studies of capecitabine [23, 24].

The present study identified no consistent or clinically significant differences in the PK profiles of capecitabine metabolites, including 5-FU (the active antitumor metabolite), when capecitabine was administered concurrently with trastuzumab or cisplatin. In phase I studies evaluating the combination of capecitabine with paclitaxel [18] and docetaxel [25], the PK profiles of capecitabine and its metabolites were found to be unaffected by either drug. The data in the present study (Table 2) are in accordance with those reported previously [14, 18], showing that 5′-DFUR is the major circulating anabolite. Upon administration, capecitabine is hydrolyzed by carboxylesterase (primarily in the liver) to form 5′-DFCR. This is then converted to 5′-DFUR by cytidine deaminase, which is highly active in tumor cells and in the liver. Finally, thymidine phosphorylase, which is significantly more active in tumor tissue than in healthy tissue, converts 5′-DFUR to 5-FU [13, 14]. The dose-normalized AUC_{last} values for capecitabine, 5-FU, and FBAL, in both the XP and HXP arms of the present study, are similar to those previously observed in a Japanese phase II gastric cancer study [17]. These data indicate that trastuzumab and cisplatin do not affect the metabolism of capecitabine. This could be due to distinctive metabolic pathways for respective drugs.

Another study [11] highlighted that the presence of cisplatin with capecitabine could result in the accumulation of 5′-DFUR and 5-FU during multiple treatment cycles because 5′-DFCR (the precursor of 5′-DFUR) is excreted mainly via the kidney, an organ particularly sensitive to the presence of cisplatin [16]. In the event of renal toxicity resulting from cisplatin administration, the AUC values of 5′-DFUR and 5-FU might increase significantly throughout the course of treatment with co-administered capecitabine, as in the previous study [11]. Increased AUC values of 5′-DFCR and 5′-DFUR may result in a higher incidence of grade 3 or 4 peripheral neuropathy, hand–foot syndrome, and diarrhea.

In conclusion, there are no consistent or clinically significant changes in the PK profile of capecitabine or cisplatin when co-administered with trastuzumab. Variability in the AUC_{last} and C_{max} values for capecitabine was consistent with the known PK profile of capecitabine and fell within established limits. Concurrent trastuzumab therapy is unlikely to alter the PK or safety profile of capecitabine or cisplatin in Japanese patients with HER2-positive AGC.

Acknowledgments The authors would like to thank the patients who participated in this trial. Editorial support was provided by Health Interactions, with funding from Roche. This study was sponsored by Chugai Pharmaceutical Co., Ltd.

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Int J Clin Oncol (2013) 18:10–16
DOI 10.1007/s10147-011-0335-y

ORIGINAL ARTICLE

Comparison of safety and efficacy of S-1 monotherapy and S-1 plus cisplatin therapy in elderly patients with advanced gastric cancer

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Received: 15 July 2011 / Accepted: 23 September 2011 / Published online: 22 October 2011

Abstract
Background Although S-1 plus cisplatin (SP) therapy is recognized as the standard treatment for advanced gastric cancer (AGC) in Japan, its safety and efficacy in elderly patients have not been investigated sufficiently.
Methods We retrospectively reviewed the data of 58 patients with AGC selected from 82 consecutive patients who were ≥70 years old and were treated with SP or S-1 monotherapy as the first-line therapy. In SP, S-1 (40 mg/m^2, bid) was administered for 3 weeks and cisplatin (60 mg/m^2) on day 8, every 5 weeks. In S-1 monotherapy, S-1 (40 mg/m^2, bid) was administered for 4 weeks, every 6 weeks.
Results SP and S-1 was administered in 21 and 37 patients, respectively. There were some differences in patient characteristics between the treatment groups, such as histological type ($P = 0.16$); the presence of liver metastasis ($P = 0.07$); and the presence of peritoneal metastasis ($P = 0.02$). The incidences of grade 3/4 hematological toxicities were 57% (12/21) in the SP and 35% (13/37) in the S-1 group ($P = 0.17$). Those of non-hematological toxicities were 14% (3/21) and 14% (5/37) for anorexia, 10% (2/21) and 14% (5/37) for fatigue, and 5% (1/21) and 5% (2/37) for nausea in the SP and S-1 groups, respectively. Median progression-free survival and median overall survival in the SP and S-1 groups were 5.0 and 5.2 months, and 14.4 and 10.9 months, respectively.
Conclusion SP and S-1 therapy were both feasible in elderly patients, though there is the risk of a high incidence of hematological toxicities.

Keywords S-1 · Cisplatin · Elderly · Feasibility · Efficacy

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Introduction

With more than 800,000 new cases per year reported globally, gastric cancer is the second most common cause of cancer death [1, 2]. Systemic chemotherapy prolongs survival and improves quality of life in patients with advanced gastric cancer (AGC), compared to the best supportive care provided alone [3–5]. In Japan, the combination chemotherapy of S-1 plus cisplatin (SP) is recognized as a standard treatment for AGC from the results of pivotal phase III studies [6–8].

The population of elderly patients is increasing rapidly all over the world, and age is the most significant risk factor for the survival of various kinds of cancer patients [9]. However, it is uncertain whether evidence on the safety and efficacy of treatments from clinical trials is also

applicable to patients who are 70 years or older, because the proportion of elderly patients included in most clinical trials is small: patients over 70 years old accounted for less than 25% in the Japan Clinical Oncology Group (JCOG) 9912 trial [6] and only 17% in the S-1 plus cisplatin versus S-1 alone for first-line treatment of AGC (SPIRITS) trial, which compared SP therapy to S-1 monotherapy alone [7]. The subset analysis of the SPIRITS trial showed that the hazard ratio for overall survival in elderly patients between 70 and 74 years old was 0.95, while that in the whole study population was 0.77. Therefore, a different treatment strategy might be necessary for elderly cancer patients.

In the present single-institution retrospective study, we assessed the safety and efficacy of SP therapy and S-1 monotherapy in elderly patients with AGC.

Materials and methods

Patients

The subjects of this study were patients with unresectable or recurrent gastric cancer who received SP therapy or S-1 monotherapy at the Shizuoka Cancer Center between September 2002 and March 2008. The patient selection criteria were as follows: age 70 years or older; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; histologically proven adenocarcinoma; absence of history of prior chemotherapy; adequate oral intake; adequate bone marrow, renal, and hepatic functions (absolute neutrophil count of 1,500/μl or more, platelet count 10,000/μl or more, serum creatinine of 1.5 mg/dl or less, serum transaminase levels less than 100 IU/l or less than 200 IU/l if hepatic metastasis existed); presence of at least one non-curative factor other than positive peritoneal washing cytology; and absence of concomitant malignancy. A measurable lesion was not mandatory.

Treatment dose and schedule

In SP therapy, S-1 was administered orally at a dose of 40 mg/m^2 bid on day 1 through day 21 followed by 14 days of rest, with cisplatin 60 mg/m^2 being administered intravenously on day 8. This regimen was repeated every 35 days until detection of disease progression, appearance of unacceptable toxicities, or the patient's refusal to continue treatment. In S-1 monotherapy, S-1 40 mg/m^2 bid was administered on day 1 through day 28, followed by 14 days of rest, until any of the above-mentioned events occurred. In each treatment group, the dose of S-1 was determined according to the body surface area (BSA), as follows: 40 mg bid for BSA less than 1.25 m^2; 50 mg bid for BSA 1.25–1.5 m^2; 60 mg bid for BSA over 1.5 m^2.

These treatments were administered according to standard clinical practice. All physicians generally adhered to the following treatment modification criteria. If a grade 3 or higher adverse event, grade 2 increase of creatinine, or grade 2 infection occurred, treatment was suspended during the cycle or the start of the subsequent cycle was delayed until recovery of non-hematological toxicities grade 1 or lower, the neutrophil count reached more than 1,500/μl, and the platelet count reached more than 7.5 × 10^4/l. The dose of S-1 and cisplatin was reduced if any of the following adverse drug reactions occurred during the previous cycle: grade 4 leukocytopenia, anemia, or thrombocytopenia; or grade 3 or higher non-hematological toxicities.

Efficacy and toxicity evaluation

We retrospectively obtained all the clinical data from the medical records. Physical examinations and laboratory tests were repeated at least once every 3 weeks. Data on adverse events were collected until 30 days from the last administration or initiation of the subsequent chemotherapy, whichever occurred earlier. We evaluated adverse events on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Response evaluation was repeated at least once every 2 months. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Statistical analysis

Differences in the distribution of variables were evaluated using the Fisher exact test or Mann–Whitney *U* test, as appropriate. Patients who did not have a target lesion were excluded from the response analysis.

Overall survival (OS) was defined as the period from the date of the first administration of S-1 to the date of death from any cause or to the last date of confirmation that the patient was alive in the census. Progression-free survival (PFS) was defined as the period from the date of the first administration of S-1 to the earliest date of detection of tumor progression by imaging, or symptomatic deterioration clinically judged to be caused by disease progression, or the last date that the patient was confirmed to be alive without disease progression in the census. Survival curves were drawn by the Kaplan–Meier method.

The following variables were examined in the univariate analysis of OS and PFS: treatment, age, sex, PS, presence of complications, prior gastrectomy, creatinine clearance, histological type, presence of target lesions, number of metastatic sites, presence of liver metastasis, peritoneal metastasis, and lymph node metastasis. Multivariate analysis included potentially predictive variables for the risk of

disease progression or death in univariate analysis. $P < 0.05$ was considered significant.

All statistical analyses were performed using Dr. SPSS II (SPSS Japan Inc., Japan). Written informed consent was obtained from all the patients before starting the chemotherapy.

Results

Patient characteristics

A total of 82 consecutive patients with gastric cancer who were 70 years or older received SP therapy or S-1 monotherapy between September 2002 and March 2008 at the Shizuoka Cancer Center. Among them, 24 patients were excluded for the following reasons: absence of non-curative factor other than positive peritoneal washing cytology (10 patients), organ dysfunction (7 patients), absence of histological confirmation of adenocarcinoma (6 patients), and concomitant malignancy (1 patient). Therefore, 58 patients were included as subjects in this study; of them, 21 patients were treated with SP therapy and 37 were treated with S-1 monotherapy.

Patient characteristics are shown in Table 1. There were some differences in background between subjects in the SP and S-1 groups, such as histologically determined intestinal type (48 vs. 62%, respectively; $P = 0.16$); the presence of liver metastasis (57 vs. 32%, respectively; $P = 0.07$); and the presence of peritoneal metastasis (14 vs. 43%, respectively; $P = 0.02$).

Table 1 Patient backgrounds

	SP group	S-1 group	*P* value
Number of patients	21	37	
Age (years), median (range)	73 (70–82)	73 (70–80)	0.51
Age ≤75	17 (81%)	25 (68%)	0.27
Age >75	4 (19%)	12 (32%)	
Sex			0.97
Male	16 (76%)	28 (76%)	
Female	5 (24%)	9 (24%)	
ECOG performance status			0.78
0	7 (33%)	14 (38%)	
1	13 (62%)	21 (57%)	
2	1 (5%)	2 (5%)	
Complications			0.28
+	10 (48%)	23 (62%)	
−	11 (52%)	14 (38%)	
Prior gastrectomy			0.82
+	9 (43%)	17 (46%)	
−	12 (57%)	20 (54%)	
Creatinine clearance			0.60
Median (range) (ml/min)	63.2 (40–125.8)	63.9 (35.9–98.7)	
Histological type			0.16
Intestinal	10 (48%)	23 (62%)	
Diffuse	11 (52%)	14 (38%)	
Tumor status			0.22
Metastatic	14 (67%)	30 (81%)	
Recurrent	7 (33%)	7 (19%)	
Metastatic sites			
Liver	12 (57%)	12 (32%)	0.07
Peritoneum	3 (14%)	16 (43%)	0.02
Lymph node	14 (66%)	21 (57%)	0.46
Target lesions			0.65
+	18 (86%)	30 (81%)	
−	3 (14%)	7 (19%)	
Number of metastatic sites			0.64
0	1 (5%)	0 (0%)	
1	7 (33%)	13 (35%)	
2	11 (52%)	19 (51%)	
≥3	2 (10%)	5 (14%)	

Exposure to treatment

The median number of treatment cycles for SP was 3 (range 1–8) and for S-1 was 4 (range 1–18). Treatment modification was required in 11 SP patients (52%) and in 21 S-1 patients (57%) as follows: dose reduction in 3 patients (14%) and in 14 patients (38%), and delay of the subsequent cycle in 9 patients (43%) and in 14 patients (38%), respectively. Both dose reduction and subsequent cycle delay were required in 1 SP patient and in 7 S-1 patients. The median relative dose intensity per patient of S-1 and cisplatin was 80% (range 42–96%) and 82% (range 55–100%), respectively, in the SP group, and that of S-1 was 86% (range 54–100%) in the S-1 group. The main reason for treatment failure was disease progression in both treatment arms: 76% in SP and 92% in S-1 groups. In addition, 19% of patients in the SP group stopped treatment because of adverse events.

Adverse events

The adverse events are shown in Table 2. The incidences of grade 3 or higher hematological toxicities were greater in the SP group (12/21: 57%) than in the S-1 group (13/37: 35%), although the difference was not statistically significant ($P = 0.10$). Incidences of specific hematological toxicities for the SP and S-1 groups were 33% (7/21) and 5% (2/37) for neutropenia, 43% (9/21) and 32% (12/37) for anemia, and 19% (4/21) and 0% (0/37) for thrombocytopenia, respectively. The incidence of grade 3 or higher

non-hematological toxicities was similar in both treatment groups: 14% (3/21) and 14% (5/37) for anorexia, 10% (2/21) and 14% (5/37) for fatigue, and 5% (1/21) and 5% (2/37) for nausea in the SP and S-1 groups, respectively. The median creatinine clearance calculated by the Cockcroft–Gault equation was 53.4 and 56.0 ml/min, respectively, in the 10 patients of SP and 14 of S-1 who experienced grade 3 or 4 toxicity (excluding that of anemia). The median creatinine clearance was 64.1 and 66.8 ml/min in patients who did not experience grade 3 or 4 toxicity in the SP and S-1 groups, respectively.

One patient from each treatment group died within 30 days of the last administration of chemotherapy. One was a 74-year-old man from the SP group, who started S-1 at the standard dose after palliative total gastrectomy. After administration of cisplatin on day 8, he received hydration therapy from day 11 to 14 for the treatment of anorexia (grade 2) and diarrhea (grade 1). After recovering from these symptoms, he was discharged from the hospital on day 15. On day 18, he suffered from diarrhea again, and was admitted to another hospital. Despite intensive care, he died on day 27 because of arrythmia. In this case, the possibility of treatment-related death could not be excluded, because dehydration due to severe diarrhea might have caused the arrythmia. The other patient from the S-1 group was a 74-year-old man who presented after gastrojejunostomy for obstruction due to the primary tumor. He received the standard dose of S-1, and visited our hospital on days 15 and 29 in the first cycle without any serious adverse events. However, he was found dead at home on day 38. He had no specific concomitant disease except mild hypertension. The cause of death was diagnosed as acute heart failure, and it is possible that S-1 contributed to his death.

Table 3 Response in patients with target lesions

	SP group ($n = 18$)	S-1 group ($n = 30$)
Best overall response		
CR	1	2
PR	8	12
SD	3	8
PD	6	7
NE	0	1
Response proportion (%)	50.0	46.7

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluated

Response and survival

Eighteen patients in the SP group and 30 in the S-1 group had measurable lesions. The objective response rate was 9/18 (50.0%) in the SP group and 14/30 (46.7%) in the S-1 group. Among the responders, complete response was obtained in one patient in the SP group and 2 in the S-1 group (Table 3).

Twenty-one patients in the SP group and 37 in the S-1 group were involved in the PFS and OS analysis. The curves of PFS and OS for the SP and S-1 groups almost overlapped (Figs. 1, 2). The median PFS was 5.0 months in the SP group and 5.2 months in the S-1 group [hazard ratio (HR): 1.18, 95% confidence interval (CI): 0.68–2.06]. The median survival time (MST) was 14.4 months in the SP group and 10.9 months in S-1 (HR: 0.99, 95% CI: 0.57–1.71). The proportion of patients who received subsequent chemotherapy was similar in the SP and S-1 groups: 62% (13/21) and 65% (24/37), respectively.

Table 2 Adverse events

	SP group ($n = 21$)				S-1 group ($n = 37$)			
	G1/2	G3	G4	≥G3 (%)	G1/2	G3	G4	≥G3 (%)
Hematological								
Leukocytopenia	8	5	1	29	16	1	0	3
Neutropenia	7	5	2	33	8	2	0	5
Anemia	12	5	4	43	24	12	0	32
Thrombocytopenia	12	3	1	19	8	0	0	0
Non-hematological								
Febrile neutropenia	–	0	0	0	–	0	0	0
Fatigue	10	1	1	10	16	5	0	14
Anorexia	16	2	1	14	18	5	0	14
Diarrhea	5	1	0	5	12	0	0	0
Stomatitis	4	0	0	0	13	1	0	3
Nausea	11	1	0	5	9	2	0	5
Vomiting	2	0	0	0	6	0	0	0

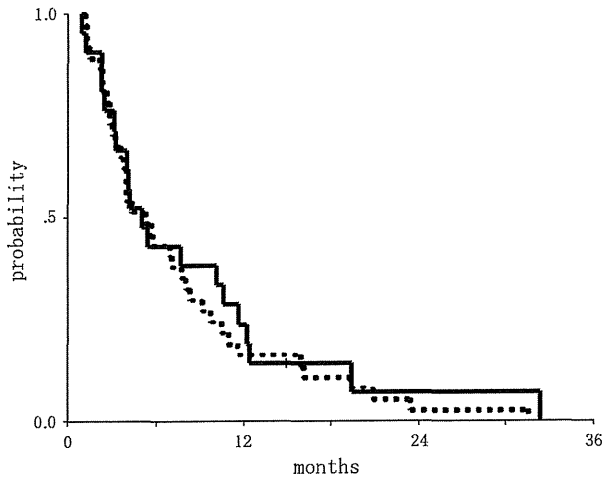

Fig. 1 Progression-free survival (PFS). The median PFS was 5.0 months in the SP group ($n = 21$, *solid line*) and 5.2 months in the S-1 group ($n = 37$, *dotted line*). The hazard ratio was 1.18, and the 95% confidence interval was 0.68–2.06

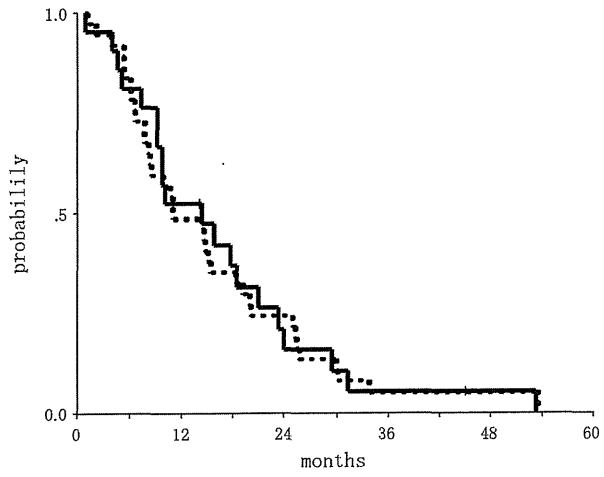

Fig. 2 Overall survival (OS). The median survival time was 14.4 months in the SP group ($n = 21$, *solid line*), and 10.9 months in the S-1 group ($n = 37$, *dotted line*). The hazard ratio was 0.99, and the 95% confidence interval was 0.57–1.71

Multivariate analysis showed that poor PS was the only factor associated with shorter OS (HR: 2.12, 95% CI: 1.37–3.26, $P = 0.001$) among the three potentially predictive variables selected by univariate analysis (age, PS, presence of peritoneal metastasis), while there was no predictive variable for PFS.

Discussion

Following the results of pivotal phase III trials, SP therapy is considered the standard chemotherapy in patients with unresectable or recurrent gastric cancer in Japan [6–8]. In the SPIRITS trial, the survival benefit of SP therapy over S-1 monotherapy was demonstrated with acceptable toxicity levels; however, the subset analysis showed that the hazard ratio in patients who were 70 years or older was 0.95 (95% CI: 0.71–1.27) [7]. However, because the subset analysis contained only 50 patients (17%) who were 70 years or older, there is uncertainty about the superiority of SP therapy over S-1 monotherapy in elderly patients with AGC. Thus, further investigation of SP therapy and S-1 monotherapy in elderly gastric cancer patients is necessary.

Because this study was retrospective, patient backgrounds between the two groups were not well balanced. In the S-1 group, the proportion of patients with peritoneal metastasis was significantly higher than in the SP group. Peritoneal metastasis is generally considered to be one of the unfavorable factors relating to shorter survival time in AGC; the patients included in the prognostic model had radiologically evident peritoneal metastasis or massive ascites [10]. In contrast, in the subset analysis of the JCOG 9912 trial, excluding the patients with severe peritoneal metastasis, patients without measurable lesions, mainly those with mild peritoneal metastasis, survived longer than those with measurable lesions [6]. Furthermore, in a randomized phase II study comparing S-1 and capecitabine, for which eligibility criteria included adequate oral intake, peritoneal metastasis was not a prognostic factor for OS [11]. Therefore, controversy exists over whether or not peritoneal metastasis is a prognostic factor in AGC. In our study, peritoneal metastasis was diagnosed in 10 out of 16 patients in the S-1 group and in 1 out of 3 patients in the SP group by laparotomy, not by radiological assessment. Because all patients had adequate oral intake, the peritoneal metastasis of most patients in this study was not so severe (only one patient had massive ascites), and therefore we consider that the presence or absence of peritoneal metastasis may not have had a major impact on survival. In the present study, the response rates in the SP and S-1 groups were 50.0 and 46.7%, respectively, and MST was 14.4 and 10.9 months, respectively. Though MST seemed longer in the SP group, the Kaplan–Meier curves of both treatment groups almost overlapped, and the hazard ratio was 0.98 (95% CI: 0.57–1.69). This hazard ratio of SP therapy over S-1 monotherapy was very similar to that of the subset analysis of elderly patients in the SPIRITS trial [7].

The relative dose intensity in the SP and S-1 groups was over 80% for each drug. Dose reduction was required in 14% of SP group subjects and 38% of S-1 group subjects. Though there was a higher incidence of grade 3 or 4 hematological toxicities in the SP group than the S-1 group, only one patient of SP needed dose reduction because of hematological toxicity. Most dose modifications were required because of non-hematological toxicities, the incidences of which were similar between the SP group and