is expected to improve long-term prognoses. The Japan Clinical Oncology Group (JCOG) has conducted two multicenter phase II trials to evaluate the efficacy and safety of S-1 plus cisplatin as a neoadjuvant regimen and has reported promising results [7, 8].

Three criteria for evaluating tumor responses to chemotherapy are currently available. The Response Evaluation Criteria in Solid Tumors (RECIST) is the gold standard in the evaluation of tumor response, but it requires the presence of a measurable lesion [9]. Because resectable gastric cancer seldom has measurable lesions, we cannot use RECIST in the neoadjuvant setting. The Japanese Classification of Gastric Carcinoma (JCGC) includes a response evaluation criterion involving barium X-ray or endoscopic examination, which is useful for tumors without measurable lesions [10]. Furthermore, we can evaluate tumor response histologically in resected specimens. As there have been no studies comparing the validities of these radiologic and histological criteria, we have conducted this correlative study (JCOG0507-A) to find the best surrogate endpoint for overall survival in neoadjuvant studies for gastric and esophageal cancers. In esophageal cancer patients, we had reported that histological response rate was the better surrogate endpoint for survival than RECIST response rate [11]. This article reports the results for gastric cancer, comparing RECIST, JCGC, and histological criteria.

Methods

Patient population

We included all eligible patients from two clinical trials (JCOG0210 and JCOG0405) that were conducted by the JCOG. These phase II trials aimed to evaluate the efficacy and safety of neoadjuvant S-1 plus cisplatin in gastric cancer patients [7, 8]. The eligibility criteria of the JCOG0210 trial included linitis plastica (Borrmann type 4) and ulcero-invasive-type (Borrmann type 3) tumors. In the case of ulcero-invasive tumors, the size of the primary tumor was required to be 8 cm or larger. Between March 2003 and December 2003, 49 eligible patients were enrolled in the JCOG0210 trial. Responses to neoadjuvant chemotherapy were evaluated using JCGC criteria. After preoperative chemotherapy, 41 patients could undergo gastrectomy, which provided tissue samples for use in assessing the histological response to preoperative chemotherapy. Six patients failed in simple laparotomy because of the presence of incurable lesions. Two patients did not undergo surgery for reasons of chemotherapy-related death in one patient and refusal of any protocol treatment in one patient.

The eligibility criteria for the JCOG0405 trial included gastric cancer with paraaortic nodal metastases or bulky lymph nodes. Between February 2005 and June 2007, 51 eligible patients were enrolled in the JCOG0405 trial. Responses to neoadjuvant chemotherapy were evaluated with RECIST. After preoperative chemotherapy, 48 patients could undergo gastrectomy, which provided material to evaluate the histological response to preoperative chemotherapy. Three patients did not undergo surgery because of progressive tumor.

All patients in the JCOG0210 and the JCOG0405 trials gave written informed consent. These trials were approved by the JCOG Clinical Trial Review Committee and the institutional review board of each institution involved. Permission for the secondary use of trial data was included in patients' informed consent for JCOG0210 and JCOG0405. The protocol of this correlative study (JCOG0507-A) was approved by the JCOG Protocol Review Committee. JCOG0405 is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/), identification number C000000094.

Treatments

The same chemotherapy regimen was used in each of the two trials. S-1 was given orally at 80 mg/m^2 for the first 3 weeks of a 4-week cycle. Cisplatin was given as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle. Patients received two 4-week cycles of neoadjuvant S-1 plus cisplatin and then underwent gastrectomy with D2 (in the JCOG0210 trial) or D2 plus paraaortic lymphadenectomy (in the JCOG0405 trial). If curative resection was considered difficult after the second course, addition of a further course of chemotherapy before surgery was permitted only in the JCOG0405 trial. After surgery, no further treatment was given until tumor recurrence.

Response evaluation

After the second course of neoadjuvant chemotherapy, tumor response was evaluated with JCGC criteria based on computed tomography (CT), barium X-ray, and endoscopic examination findings in the JCOG0210 trial, whereas response evaluation using RECIST in the JCOG0405 trial was based only on CT findings. These evaluations were performed by the central reviewers. Response evaluations based on RECIST were not conducted in the JCOG0210 trial because many patients did not have measurable lesions. We could not evaluate the JCGC response in the JCOG0405 trial because barium X-rays and endoscopic examinations were not performed after neoadjuvant chemotherapy.

With the JCGC criteria, overall tumor response depends on the combined responses of primary gastric lesions and metastatic lesions. The details of the JCGC criteria have been described elsewhere [10]. Briefly, morphological changes of gastric lesions are evaluated by X-ray or endoscopic examinations, and the overall responses are classified into four categories: complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). Measurable lesions with at least a 50 % decrease in total tumor size in two dimensions and at least a 30 % decrease in total tumor size in one dimension are classified as PR. Evaluable but nonmeasurable lesions with flattening on X-ray or endoscopic examination, or diffusely infiltrating lesions with at least 50 % enlargement of the gastric lumen in the tumor area by X-ray examination, are also classified as PR. CR or PR cases were treated as responders.

Surgical specimens were assessed histologically, and tumor response was evaluated according to the histological criteria of the JCGC [12]. Briefly, histological evaluations were classified into five categories according to the proportion of the tumor affected by degeneration or necrosis: grade 3, no viable tumor cells remain; grade 2, viable tumor cells remain in less than 1/3 of the tumorous area; grade 1b, viable tumor cells remain in more than 1/3 but less than 2/3 of the tumorous area; grade 1a, viable tumor cells occupy more than 2/3 of the tumorous area; grade 0, no evidence of treatment effect. A histological responder was defined as a patient in whom one third or more of the tumor was affected (grade 1b, 2, or 3). Because the definition of histological responder is controversial, we also evaluated the results when a histological responder was classified as grade 2 or 3. Patients who did not undergo surgery were regarded as non-responders. These evaluations were performed by the pathologists at each institution.

Statistical analysis

The data from all eligible patients were analyzed in this study. Cases in which the tumor was not resected or could not be evaluated were treated as non-responders. With the methods used in this study, a comparison of the overall survival between responders and non-responders was said to have a pitfall because early death cases were classified into the non-responder group. In our study, however, there were no early deaths during the protocol treatment, which implies that minimal bias was induced by the classification system employed in our study.

The relationship of response and overall survival was evaluated using hazard ratios (HRs). The HR for death of responders to non-responders was estimated using the Cox proportional hazard model, and survival distributions were compared using the log-rank test. The difference in response rates between short- and long-term survivors was estimated and tested with Fisher's exact test. Statistical analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The clinicopathological characteristics of all eligible patients in the JCOG 0210 and 0405 trials are shown in Table 1. The proportion of male patients in the JCOG0405 trial was higher than that in the JCOG0210 trial. The majority of tumors were of the undifferentiated type in the JCOG0210 trial, whereas the differentiated type was more frequent in the JCOG0405 trial. Pathological node-negative (pN0) patients comprised 16 % of both the JCOG0210 (8 of 49) and JCOG0405 (8 of 51) trial populations.

Response rates

The responses to neoadjuvant S-1 plus cisplatin as evaluated by the JCGC, RECIST, and histological criteria are shown in Table 1. The response rates in the JCOG0210 trial were 57 % [95 % confidence interval (CI), 42–71 %] with the JCGC criteria and 47 % (95 % CI, 33–62 %) with histological criteria. The response rates in the JCOG0405 trial were 65 % (95 % CI, 50–78 %) with the RECIST and 51 % (95 % CI, 37–65 %) with histological criteria.

Survival curves in responders and non-responders

Overall survival curves for the JCOG0210 trial are shown in Fig. 1. The difference of the 3-year overall survival rate between responders and non-responders was 17.8 % (responders, 32.1 %; non-responders, 14.3 %) on JCGC criteria and 27.6 % (responders, 39.1 %; non-responders, 11.5 %) on histological criteria. The HR for death of histological responders to non-responders (0.40; 95 % CI, 0.20–0.77) was lower than that using JCGC criteria (0.54; 95 % CI, 0.28–1.03), and the log-rank P value on histological criteria ($P = 0.005$) was much smaller than that on JCGC criteria ($P = 0.059$).

Overall survival curves for the JCOG0405 trial are shown in Fig. 2. The difference in the 3-year overall survival rate between responders and non-responders was 5.0 % (responders, 60.6 %; non-responders, 55.6 %) on RECIST and 29.1 % (responders, 73.1 %; non-responders, 44.0 %) on histological criteria. The HR for death of histological responders to non-responders (0.39; 95 % CI, 0.17–0.94) was lower than that using the RECIST (0.67;

Table 1 Patient characteristics

	JCOG0210 ($n = 49$)	JCOG0405 ($n = 51$)
Age (years)		
Median	61	63
Range	32–75	42–75
Gender		
Male	28	42
Female	21	9
Borrmann macroscopic type		
0	0	2
1	0	1
2	0	15
3	20	31
4	29	0
5	0	2
Histology		
Differentiated	9	28
Undifferentiated	40	22
Unknown	0	1
Clinical T stage		
cT1	0	1
cT2	2	10
cT3	45	38
cT4	2	2
Clinical N stage		
cN0	16	0
cN1	20	0
cN2	13	25
cN3	0	26
Residual tumor		
R0	31	42
R1 or R2	10	6
Unresected	8	3
Pathological T stage		
pT0	1	2
pT1	4	7
pT2	11	23
pT3	18	15
pT4	7	1
Unresected	8	3
Pathological N stage		
pN0	8	8
pN1	10	5
pN2	16	21
pN3	7	14
Unresected	8	3
Tumor responses evaluated by the JCGC criteria		
CR	0	–
PR	28	–
NC	13	–
PD	3	–
NE	5	–
Tumor responses evaluated by the RECIST		
CR	–	0
PR	–	33
SD	–	14
PD	–	4
Tumor responses evaluated by the histological criteria of the JCGC		
Grade 3	1	1
Grade 2	12	13
Grade 1b	10	12
Grade 1a	9	19
Grade 0	9	3
Unresected	8	3

T stage and N stage were according to the 13th edition of the Japanese Classification of Gastric Carcinoma

JCGC Japanese classification of gastric carcinoma, *CR* complete response, *PR* partial response, *NC* no change, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

95 % CI, 0.29–1.56), and the log-rank P value on histological criteria ($P = 0.030$) was much smaller than that on RECIST ($P = 0.35$).

When a histological responder was classified as grade 2 or 3, the HRs for death of modified histological responders to non-responders were 0.57 (95 % CI, 0.26–1.25) in the JCOG0210 trial and 0.32 (95 % CI, 0.09–1.08) in the JCOG0405 trial. The log-rank P values on modified histological criteria were 0.15 in the JCOG0210 and 0.067 in the JCOG0405.

Response rates in short- and long-term survivors

Because the median overall survival time in all eligible patients in the JCOG0210 was 17.3 months, we divided patients into short- and long-term survivors with a cutoff for overall survival time of 18 months. The respective response rates based on JCGC and histological criteria were 46 % and 31 % in short-term survivors and 70 % and 65 % in long-term survivors (Fig. 3). The difference in response rates between short- and long-term survivors using histological criteria (Fisher's exact test, $P = 0.023$) was greater than that using JCGC criteria (Fisher's exact test, $P = 0.15$).

Although for the JCOG0405 trial the median overall survival time was not reached at the time of this analysis, the 3-year overall survival rate was 59 %. We therefore set

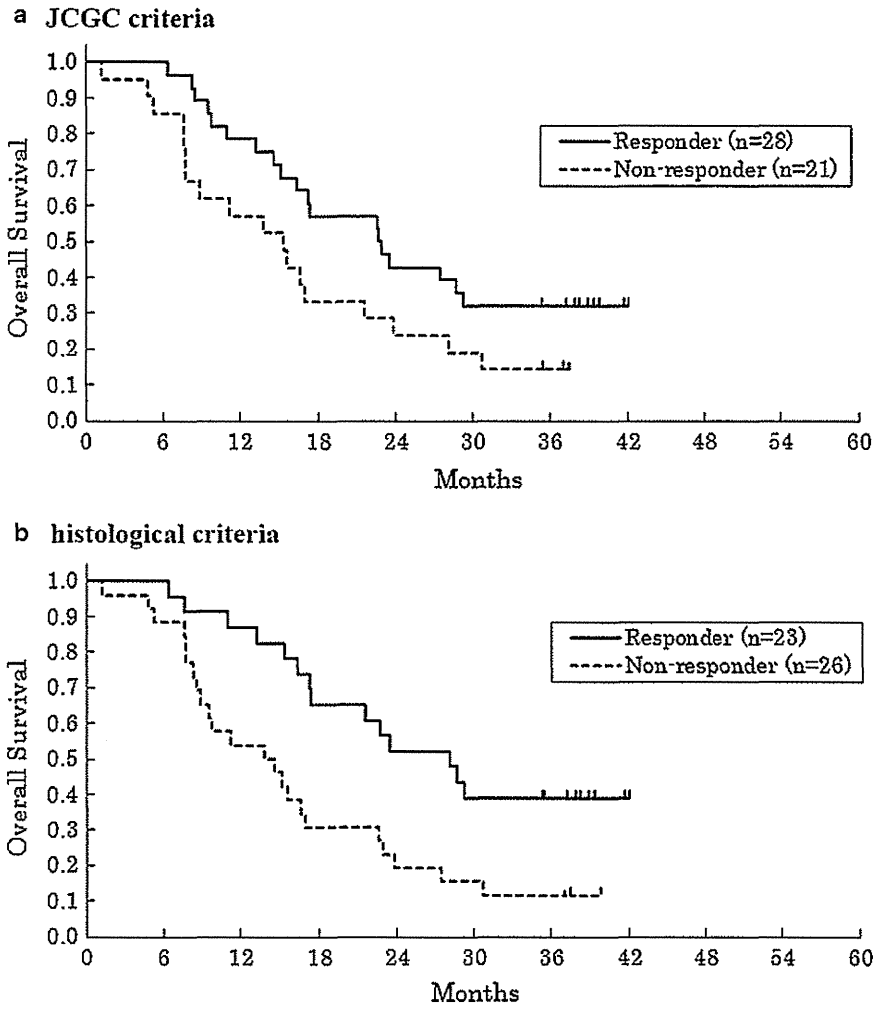

Fig. 1 Overall survival curves between responders and non-responders for the JCOG0210 trial: JCGC criteria (a), $P = 0.059$ (log-rank test); histological criteria (b), $P = 0.005$ (log-rank test)

the cutoff for overall survival time at 36 months. The respective response rates using RECIST and histological response rates were 62 % and 33 % in short-term survivors and 67 % and 63 % in long-term survivors (Fig. 4). The difference in response rates between short- and long-term survivors using histological criteria (Fisher's exact test, $P = 0.048$) was greater than that using RECIST (Fisher's exact test, $P = 0.77$).

Again, when a histological responder was classified as grade 2 or 3, the differences in response rates between short- and long-term survivors based on modified histological criteria were 16 % (Fisher's exact test, $P = 0.33$) in the JCOG0210 trial and 22 % (Fisher's exact test, $P = 0.11$) in the JCOG0405 trial.

Discussion

In this correlative study of two phase II trials, histological criteria, as compared to RECIST and JCGC criteria, demonstrated a greater difference in both overall survival between responders and non-responders and in response rates between short- and long-term survivors. This result indicates that the histological response was the best surrogate endpoint for overall survival in these neoadjuvant trials for gastric cancer, and the conclusion for gastric cancer was the same as that in esophageal cancer [11], which is very important for the development of cancer treatments. If the histological response can be used as the primary endpoint in neoadjuvant settings, we can evaluate any gastric cancer population regardless of the presence of measurable lesions.

RECIST is the gold standard in the evaluation of tumor responses, but it requires the presence of a measurable lesion. In the present version of RECIST (Ver. 1.1), the criteria for measurable lesions were revised to be stricter: a lymph node must be more than 15 mm in short-axis diameter [13]. There are many unresectable gastric cancer patients without measurable metastatic lesions, because the most frequent pattern of recurrence in advanced or

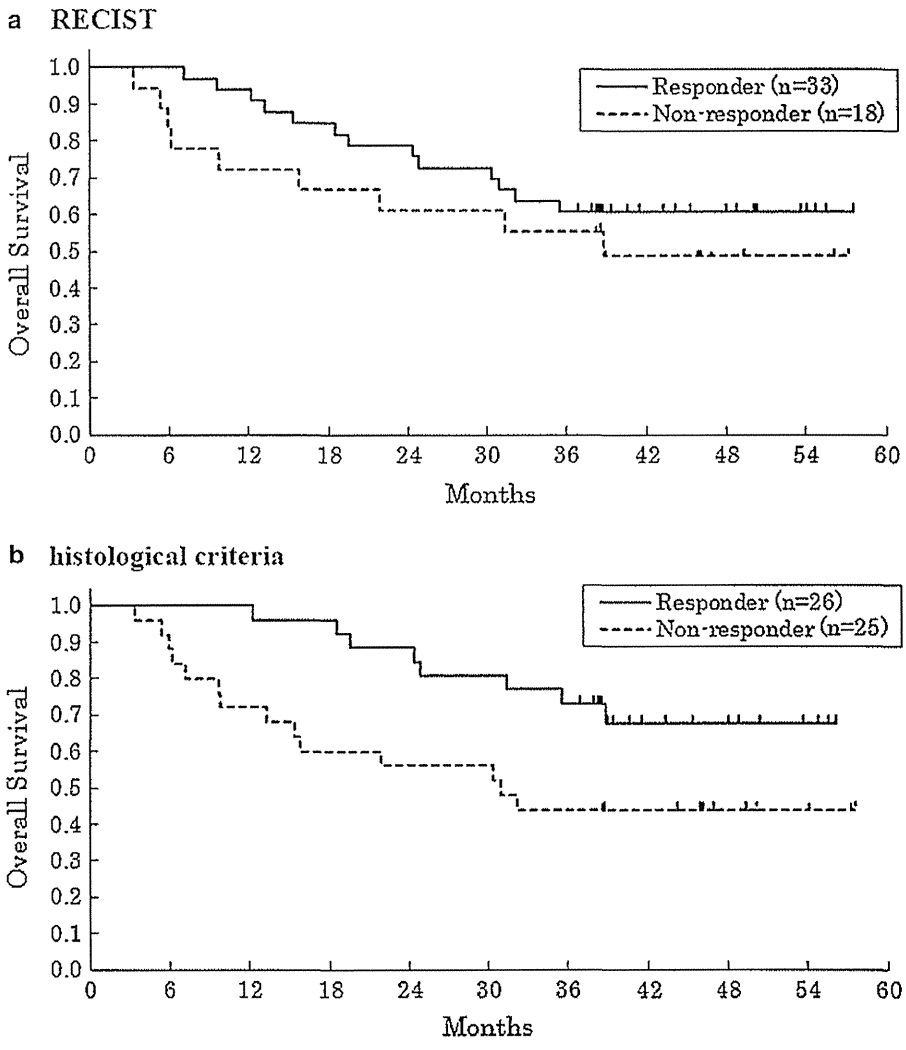

Fig. 2 Overall survival curves between responders and non-responders for the JCOG0405 trial: RECIST (a), $P = 0.35$ (log-rank test); histological criteria (b), $P = 0.030$ (log-rank test)

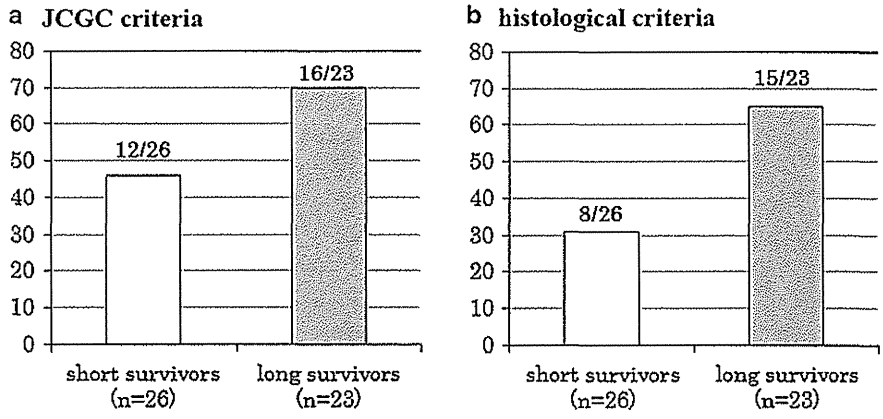

Fig. 3 Comparison of the response rates between short-term (*short survivors*) and long-term (*long survivors*) survivors for the JCOG0210 trial: JCGC criteria (a), $P = 0.15$ (Fisher's exact test); histological criteria (b), $P = 0.023$ (Fisher's exact test)

recurrent cases is peritoneal seeding. Particularly in neo-adjuvant settings, resectable gastric tumors seldom have measurable lesions. Furthermore, the primary lesion of digestive tract is not suitable for measurable lesion in terms of reproducibility, as the RECIST guideline cautioned.

The JCGC response evaluation criteria were established to evaluate tumor responses even for tumors without measurable lesions. Although it can be used for any type of gastric cancer, evaluation using endoscopic examination is subjective. Furthermore, repetition of barium X-ray or

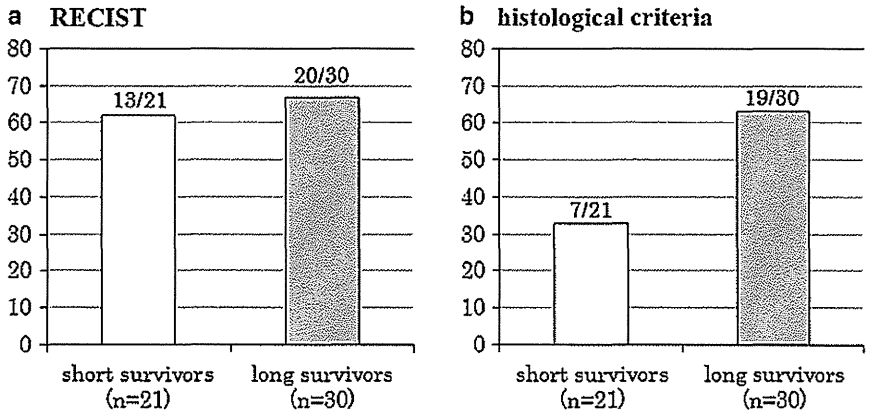

Fig. 4 Comparison of the response rates between short- and long-term survivors for the JCOG0405 trial: RECIST (a), $P = 0.77$ (Fisher's exact test); histological criteria (b), $P = 0.048$ (Fisher's exact test)

endoscopic examination for evaluation of tumor response is a significant burden for patients. In contrast, histological evaluation does not require any presurgical examination. If the histological response is indeed the most useful indicator in neoadjuvant settings, patients will not need to undergo invasive examinations after chemotherapy.

There are several different histological grading systems for the evaluation of tumor responses in addition to that defined by the JCGC. Becker et al. [14, 15] proposed the following system: tumors with no viable cells are assigned grade Ia; tumors with 1–10 % viable cells, grade Ib; tumors with 10–50 % viable cells, grade II; and tumors with more than 50 % viable cells, grade III. Ajani et al. [16, 17] proposed a grading scheme: cases showing either an absence of tumor cells or necrosis in more than 90 % of the resected tumor were classified as responders. In this study, we used the JCGC grading system, whereby cases showing viable tumor cells remain in less than two thirds are classified as responders, but for our sensitivity analysis we changed the cutoff point from two thirds to one third. Both the JCOG0210 and JCOG0405 trials showed similar results using this grading system.

This study had some limitations. First, histological evaluations were performed only by the pathologists at each institution, although response evaluations using RECIST and JCGC criteria were conducted by the central reviewers. Because histological evaluations are not completely objective, there may have been some issues with inter-rater reliability. However, our JCOG study group institutions are staffed with experts not only in surgery and chemotherapy, but also in pathology. We believe there was little heterogeneity in the histological evaluations performed by this experienced group. Another study is now ongoing to compare the predictive values based on the different scoring systems of histological response after central review by two reference pathologists. A second limitation is that this study enrolled only patients who had received preoperative S-1 plus cisplatin. S-1 plus cisplatin is one of the standard regimens for metastatic gastric cancer [18, 19]. The validity of histological tumor response evaluation may vary with different chemotherapeutic regimens, and further studies are needed to investigate this point.

In conclusion, histological response rate seemed to be a better surrogate endpoint for overall survival than radiologic response rate in studies of neoadjuvant therapy for gastric cancer.

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FULL PAPER

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Keywords: trastuzumab; S-1; cisplatin; HERBIS

Phase II study of trastuzumab in combination with S-1 plus cisplatin in HER2-positive gastric cancer (HERBIS-1)

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Background: S-1, an oral fluoropyrimidine, plus cisplatin (SP) is a standard regimen for advanced gastric cancer (AGC) in East Asia. To date, no studies have evaluated the efficacy and safety of trastuzumab combined with SP in patients with human epidermal growth factor receptor type 2 (HER2)-positive AGC.

Methods: Patients with HER2-positive AGC received S-1 (80–120 mg per day) orally on days 1–14, cisplatin (60 mg m^{-2}) intravenously on day 1, and trastuzumab (course 1, 8 mg kg^{-1}; course 2 onward, 6 mg kg^{-1}) intravenously on day 1 of a 21-day cycle. The primary end point was response rate (RR); secondary end points included overall survival (OS), progression-free survival (PFS), time to treatment failure (TTF), and adverse events.

Results: A total of 56 patients were enrolled. In the full analysis set of 53 patients, the confirmed RR was 68% (95% confidence interval (CI) = 54–80%), and the disease control rate was 94% (95% CI = 84–99%). Median OS, PFS, and TTF were estimated as 16.0, 7.8, and 5.7 months, respectively. Major grade 3 or 4 adverse events included neutropaenia (36%), anorexia (23%), and anaemia (15%).

Conclusions: Trastuzumab in combination with SP showed promising antitumour activity and manageable toxic effects in patients with HER2-positive AGC.

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Gastric cancer is the second leading cause of cancer deaths worldwide (Ferlay *et al*, 2010). A global standard regimen for to treat advanced gastric cancer (AGC) has not been established (Macdonald *et al*, 2001; Cunningham *et al*, 2008). In Western countries, regimens containing a fluoropyrimidine (fluorouracil or an oral preparation) plus a platinum compound, and usually including docetaxel or epirubicin, have been most widely used. In East Asia, including Japan and Korea, a fluoropyrimidine plus a platinum compound has been used as standard therapy (Koizumi *et al*, 2008; Kang *et al*, 2009).

Recent studies have shed new light on the molecular mechanisms underlying the development and progression of gastric cancer. Trastuzumab is a monoclonal antibody targeting human epidermal growth factor receptor type 2 (HER2) with two antigen-specific sites that bind to the juxtamembrane portion of the extracellular domain of the HER2 receptor, thereby preventing activation of its intracellular tyrosine kinase (Hudis, 2007). The Trastuzumab for Gastric Cancer (ToGA) study, an international phase III trial comparing chemotherapy consisting of cisplatin plus capecitabine or fluorouracil *vs* trastuzumab plus chemotherapy in patients with HER2-positive AGC, demonstrated a survival benefit with the addition of trastuzumab (Bang *et al*, 2010). Currently, both the US Food and Drug Administration and the European Medicines Agency approved trastuzumab for the treatment of patients with HER2-positive AGC, and trastuzumab in combination with cisplatin plus capecitabine or fluorouracil is a standard treatment for HER2-positive AGC in the West.

S-1 is a fluoropyrimidine preparation combining tegafur, a prodrug of 5-fluorouracil (5-FU), gimeracil, and oteracil potassium in a molar ratio of 1 : 0.4 : 1. Gimeracil is a dihydropyrimidine dehydrogenase inhibitor, allowing high concentrations of 5-FU to be maintained (Shirasaka *et al*, 1996; Diasio, 1999). Two phase II studies (Sakata *et al*, 1998; Koizumi *et al*, 2000) in patients with AGC showed response rates (RRs) exceeding 40%. The S-1 Plus cisplatin versus S-1 In RCT In the treatment for Stomach cancer (SPIRITS) phase III trial established S-1 plus cisplatin (SP) as a standard first-line regimen for AGC in the East (Koizumi *et al*, 2008; Japanese Gastric Cancer Association, 2011). However, SP plus trastuzumab has not been evaluated in patients with HER2-positive AGC to date. We therefore conducted this phase II study to evaluate the efficacy and safety of SP plus trastuzumab in HER2-positive AGC.

PATIENTS AND METHODS

Patients. We enrolled patients with histologically proven unresectable or recurrent HER2-positive tumours in the stomach or gastroesophageal junction. Human epidermal growth factor receptor type 2 status of tumours was evaluated using immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH). In the IHC testing, HER2 tumour cell-membrane immunostaining was scored using a four-grade scale (0/1+/2+/3+) according to scoring scheme (ToGA score): 0, no staining or membranous reactivity in $<10\%$ of tumour cells; 1+, weak, barely perceptible membranous reactivity in $>10\%$ of tumour cells; 2+, complete or basolateral membranous reactivity either nonuniform or weak in $\geqslant 10\%$ of cells; and 3+, complete or basolateral membranous reactivity of strong intensity in $\geqslant 10\%$ of tumour cells (Hofmann *et al*, 2008; Bang *et al*, 2010). FISH analyses for HER2 status were carried out according to the manufacturer's procedure. The total numbers of HER2 and chromosome 17 signals were counted in at least 20 tumour cell nuclei in two different areas. The case with HER2/chromosome 17 ratio of $\geqslant 2.0$ was defined as FISH positive. In this study, only patients with IHC 3+, or IHC 2+ and FISH positive were eligible. Patients were required to have measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Eisenhauer *et al*, 2009). Eligibility criteria also included: age between 20 and 75 years; Eastern Cooperative Oncology Group performance status score of 0 or 1; leukocyte count between 3500 and 12 000 mm^{-3}, neutrophil count $\geqslant 2000\ mm^{-3}$, hemoglobin $\geqslant 9.0\ g\ dl^{-1}$, platelet count $\geqslant 100\,000\ mm^{-3}$, serum bilirubin $<1.5\ mg\ dl^{-1}$, creatinine clearance $\geqslant 60\ ml\ min^{-1}$ calculated using the Cockcroft–Gault formula, serum creatinine $\leqslant 1.2\ mg\ dl^{-1}$, serum aspartate aminotransferase and alanine aminotransferase $<100\ IU\ l^{-1}$; and baseline left ventricular ejection fraction $\geqslant 50\%$. Patients were excluded from the study if they could not maintain sufficient oral intake, have massive ascites or pleural effusions, or had received prior chemotherapy or radiotherapy within 6 months before enrollment. The study protocol was approved by the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) Steering Committee and the institutional review boards of all participating hospitals. All patients provided written informed consent before enrollment. This study was registered with UMIN-CTR, UMIN000005739.

Treatment. Trastuzumab was commercially obtained in this study. Patients received cisplatin ($60\ mg\ m^{-2}$) plus trastuzumab (course 1, $8\ mg\ kg^{-1}$; course 2 onward, $6\ mg\ kg^{-1}$) intravenously on day 1 and oral S-1 twice daily at a dose based on body surface area ($<1.25\ m^2$, 40 mg; $\geqslant 1.25$ to $<1.5\ m^2$, 50 mg; $\geqslant 1.5\ m^2$, 60 mg) on days 1–14 of a 21-day cycle.

This schedule was repeated until disease progression, development of unacceptable toxicity, or patient withdrawal of consent. If patients had a neutrophil count less than $1000\ mm^{-3}$, platelet count less than $75 \times 10^3\ mm^{-3}$, serum creatinine more than $1.2\ mg\ dl^{-1}$, infection with fever, or anorexia, diarrhoea, oral mucositis, or rash of grade 2 or higher, treatment with S-1 was suspended. In patients with febrile neutropaenia, grade 4 neutropaenia, grade 3–4 thrombocytopaenia, serum creatinine $>1.2\ mg\ dl^{-1}$, or grade 3–4 diarrhoea, oral mucositis, or rash, doses of S-1 and cisplatin were reduced starting from the next cycle. In patients who had grade 3–4 vomiting or anorexia because of cisplatin, the dose of cisplatin was reduced. If heart failure or severe infusion reactions occurred, treatment with trastuzumab was discontinued.

Evaluations. The primary end point was RR. The secondary end points were overall survival (OS), progression-free survival (PFS), time to treatment failure (TTF), and adverse events. Tumours were assessed every 6 weeks until disease progression, and objective responses were evaluated according to the RECIST guidelines (version 1.1). For complete response (CR) or partial response (PR), confirmation 4 weeks after initial evaluation was necessary. An independent review committee assessed responses in all patients. OS was defined as the time from the date of enrollment to the date of death from any cause. PFS was defined as the time from the date of enrollment to the date of disease progression or death from any cause. TTF was defined as the time from the date of enrollment to the date when the treating physician decided to discontinue treatment for any reason. Physical examination and blood test were mandatory before each course, and left ventricular ejection fraction was assessed every 3 month during treatment. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis. The required sample size was estimated based on a threshold RR of 35% and an expected RR of 50%, 80% power, and an alpha value of 0.1 (one-sided) using the binomial test. Given 2% of ineligible patients, the target sample size was determined to be at least 50 patients. Efficacy was evaluated in all patients who received at least one dose of the study treatment.

We used the Kaplan–Meier method to estimate survival curves and Greenwood's formula to calculate 95% confidence intervals (CIs) for survival rates. Statistical analyses were conducted with R, version 3.0.1.

RESULTS

Patient background. Between July 2011 and May 2012, a total of 56 patients were enrolled from 29 hospitals in Japan. Two patients were ineligible because of inadequate renal function or the absence of measurable lesions. The characteristics of the 54 eligible patients are listed in Table 1. The median age was 66 years (range = 34–75 years). Two-thirds of patients had differentiated adenocarcinoma. Only three patients (6%) had recurrent disease; the others had unresectable lesions. The most frequent sites of metastasis were the lymph nodes (81%), followed by the liver (59%). The proportions of IHC 3+ and IHC 2+/FISH-positive tumours were 83% and 17%, respectively.

Table 1. Eligible patient characteristics

Characteristic	$n = 54$
Age, years	
Median	66
Range	34–75
Sex	
Male	42 (78%)
Female	12 (22%)
Performance status	
0	42 (78%)
1	12 (22%)
Histological type	
Differentiated	36 (67%)
Undifferentiated	18 (33%)
Previous gastrectomy	
No	45 (83%)
Yes	9 (17%)
Unresectable/recurrent	
Unresectable	51 (94%)
Recurrent with adjuvant chemotherapy	2 (4%)
Recurrent without adjuvant chemotherapy	1 (2%)
Metastatic sites[a]	
Lymph nodes	44 (81%)
Liver	32 (59%)
Lung	5 (9%)
Peritoneum	5 (9%)
Bone	2 (4%)
Other	1 (2%)
HER2 status	
IHC 3+	45 (83%)
IHC 2+/FISH positive	9 (17%)

Abbreviations: FISH = fluorescence *in situ* hybridization; HER2 = human epidermal growth factor receptor type 2; IHC = immunohistochemistry.
[a]Some patients had multiple metastatic sites.

Efficacy. Of the 54 eligible patients, 1 patient did not receive any treatment per protocol because of a decrease in serum hemoglobin levels after study enrollment. Efficacy and safety analyses were therefore conducted in the full analysis set of the remaining 53 patients.

The median number of cycles was 6 (range = 1–27), and the median relative dose intensity for S-1, cisplatin, and trastuzumab was 76%, 83%, and 96%, respectively. At the time of analysis (August 2013), 51 patients had discontinued treatment. The main reason for discontinuation was progressive disease (31 patients), followed by adverse events (16 patients). Four patients underwent surgery because of a prominent response.

The confirmed RR based on RECIST (version 1.1) was 68% (95% CI = 54–80%; 80% CI = 58–76%; Table 2), so the null hypothesis for the primary end point (RR $\leqslant$35%) was rejected ($P < 0.001$). The confirmed RRs in the differentiated type cases ($n = 35$) and the undifferentiated type cases ($n = 18$) were 69% (95% CI = 51–83%) and 67% (95% CI = 41–87%), respectively. Among 36 patients with CR or PR, the median time to response and duration of response were 41 days (range = 33–91 days) and 208 days (range = 42–630 days), respectively. The disease control rate, that is, the proportion of patients who had a CR, PR, or stable disease, was 94% (95% CI = 84–99%). Two patients (4%) had a CR. A waterfall plot of the confirmed best overall response for each patient is shown in Figure 1.

The median duration of follow-up at the time of analysis (August 2013) for the 53 patients was 13.5 months. The median OS was 16.0 months (95% CI = 13.3–not applicable), and the 1-year OS rate was 67.9% (95% CI = 56.5–81.7%; Figure 2). The median PFS was 7.8 months (95% CI = 6.0–8.8 months), and the 1-year PFS rate was 17.0% (95% CI = 9.4–30.8%; Figure 2). The median TTF was 5.7 months (95% CI = 4.2–7.1 months), and the 1-year TTF rate was 5.1% (95% CI = 1.4–18.6%).

Safety. All adverse events that occurred in three or more patients are shown in Table 3. Among the haematological adverse events, the proportions of grade 3–4 neutropaenia and anaemia were 36% and 15%, respectively. The most frequent common non-haematological toxicity was anorexia (any grade, 79%; grade 3–4, 23%). Except for anorexia, there were no grade 3 or 4 toxicities that occurred in more than 10% of patients. Creatinine was elevated in 24 of 53 patients (45%). Grade 2 infusion-related reactions occurred in three patients (6%). Heart failure did not occur in any patients.

There was one treatment-related death attributable to myelosuppression. This patient was judged as an ineligible case afterwards, because creatinine clearance before enrollment was 47.4 ml min^{-1}. Furthermore, S-1 administration continued despite a serum creatinine level of 2.31 mg dl^{-1} on day 7. Renal dysfunction led to myelosuppression that progressed to death. Upon review of the patient's records, the data and safety

Table 2. Objective response with confirmation based on RECIST

Total	$n = 53$
Complete response	2 (4%)
Partial response	34 (64%)
Stable disease	14 (26%)
Progressive disease	3 (6%)
Response rate (95% confidence interval)	68% (54–80%)
Disease control rate (95% confidence interval)	94% (84–99%)

Abbreviation: RECIST = Response Evaluation Criteria in Solid Tumor.

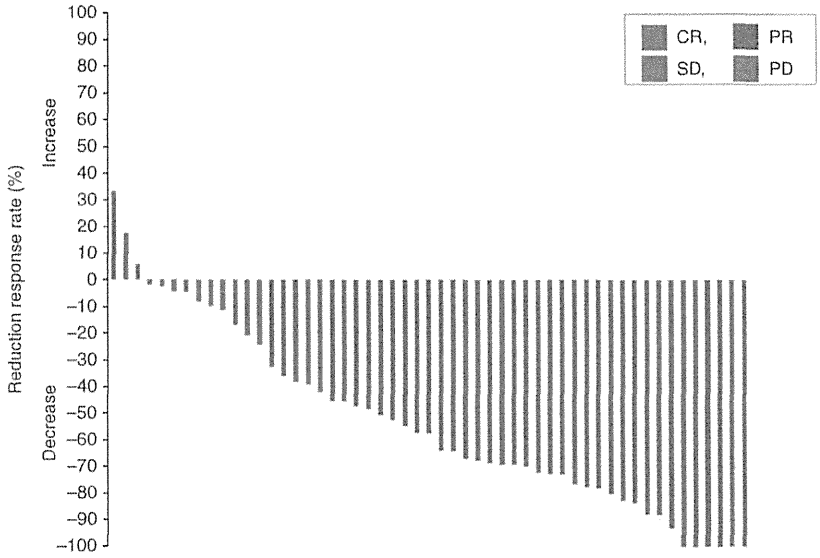

Figure 1. Waterfall plot of confirmed best overall response.

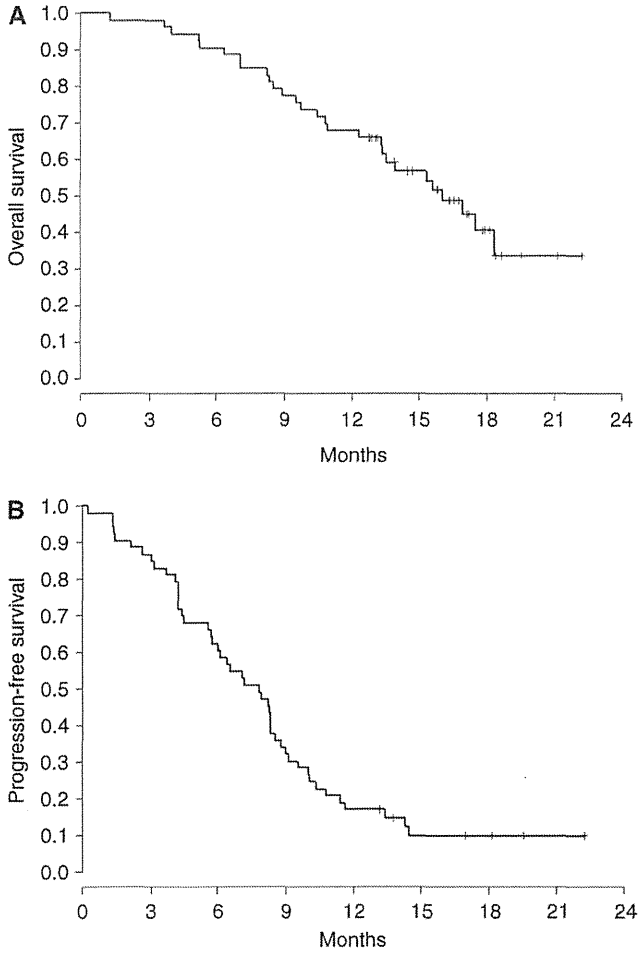

Figure 2. (A) The Kaplan–Meier overall survival and (B) progression-free survival.

monitoring committee determined that the patient died from critical deviations from the eligibility criteria and treatment protocol.

DISCUSSION

This multicenter phase II study is the first clinical trial reporting the efficacy and safety of SP plus trastuzumab in patients with HER2-positive AGC. We obtained a much higher RR (68%) than expected. The toxicity profile of our regimen was tolerable, and the incidence of grade 3–4 adverse events were similar to those of the SP regimen in the SPIRITS study (Koizumi *et al*, 2008). These results suggest that SP plus trastuzumab is a potential new treatment option for patients with HER2-positive AGC.

The ToGA study demonstrated that trastuzumab in combination with cisplatin plus capecitabine or fluorouracil was superior to cisplatin plus capecitabine or fluorouracil alone (Bang *et al*, 2010). The RR was 35% in the chemotherapy group and 47% in the trastuzumab plus chemotherapy group. In the aforementioned phase II study of a 3-week cycle of SP, the RR was 48%, compared with 68% in the present study, suggesting that trastuzumab considerably enhanced the effectiveness of chemotherapy, which is consistent with the results of the ToGA study. In addition, the median OS and PFS in our study were 16.0 and 7.8 months, respectively, whereas the subgroup of Japanese patients in the trastuzumab arm of the ToGA study had a median OS and PFS of 15.9 and 6.2 months, respectively (Sawaki *et al*, 2012). Although these results must be interpreted with caution because of the differences between the ToGA study and our study in terms of patient characteristics, especially histologic type, the proportion of patients with HER2 IHC 3+ tumours, and exclusion of patients with performance status $\geqslant 2$, trastuzumab may be a good addition to a S-1-based regimen. Experimental studies have reported that trastuzumab induces downregulation of thymidylate synthase expression. This mechanism has been implicated in the synergistic antitumour effect of S-1 plus trastuzumab against gastric cancer cell lines that overexpress HER2 (Tanizaki *et al*, 2010). Capecitabine and S-1 are both 5-FU derivatives, but were developed based on different concepts. Further studies of biomarkers and other predictors of outcomes are necessary to optimise the use of these drugs.

During the planning phase of this trial, a 5-week cycle of SP therapy was the mainstay of chemotherapy for AGC in Japan, based on the results of the SPIRITS study (Koizumi *et al*, 2008). As a molecular-targeted agent was combined with SP, the development of a 3-week cycle was planned. Results of phase II studies of a 3-week regimen of SP have been reported in gastric

Table 3. Adverse events ($n = 53$)

	Grade					
Event	1	2	3	4	Any (%)	Grade 3–4 (%)
Leukopaenia	17	18	3	1	74	8
Neutropaenia	8	5	14	5	60	36
Febrile neutropaenia	0	0	1	1	4	4
Anaemia	5	22	6	2	66	15
Thrombocytopaenia	20	6	0	0	49	0
Anorexia	15	15	12	0	79	23
Fatigue	18	14	2	0	64	4
Nausea	20	12	1	0	62	2
Hypoalbuminaemia	14	6	5	0	47	9
Hypertension	9	12	1	0	42	2
Creatinine increased	21	0	3	0	45	6
Diarrhoea	10	7	4	0	40	8
Oral mucositis	10	6	1	0	32	2
Skin rash	12	1	0	0	25	0
Vomiting	7	3	3	0	25	6
ALT increased	11	2	0	0	25	0
Constipation	7	4	0	0	21	0
Dysgeusia	7	3	0	0	19	0
AST increased	9	0	0	0	17	0
Blood bilirubin increased	6	2	0	0	15	0
Edema	6	2	0	0	15	0
Peripheral sensory neuropathy	1	5	0	0	11	0
Epistaxis	3	1	0	0	8	0
Hiccups	4	0	0	0	8	0
Fever	2	2	0	0	8	0
Infusion-related reaction	0	3	0	0	6	0
Alopecia	2	1	0	0	6	0
Abdominal pain	1	2	0	0	6	0
Skin hyperpigmentation	2	1	0	0	6	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

cancer and lung cancer (Lee *et al*, 2008; Choi *et al*, 2010; Kubota *et al*, 2010). Recently, a phase III trial comparing the standard 5-week cycle of SP with a 3-week cycle of SP was conducted in patients with AGC. This trial showed that the median PFSs in the 3-week and 5-week cycle groups were 5.5 and 4.9 months, respectively, and it concluded that a 3-week cycle of SP was superior to a 5-week cycle of SP in terms of PFS ($P = 0.042$) (Ryu *et al*, 2013). We therefore expected that a 3-week regimen of SP plus trastuzumab would be more effective than a 5-week regimen of SP plus trastuzumab. Although the dose intensity of cisplatin (20 mg m^{-2} per week) in a 3-week SP regimen was 25% lower than that (26.7 mg m^{-2} per week) in the ToGA study regimen, the RR (48%) of 3-week SP regimen was higher than that (35%) of the ToGA regimen. Thus, we considered that the dose (60 mg m^{-2}) of cisplatin was adequate in this 3-week SP regimen.

In this study, we limited subjects to patients with measurable lesions assessable according to RECIST guidelines (version 1.1). In clinical practice, however, many patients with gastric cancer have no measurable lesions, such as those with peritoneal metastasis. We are therefore conducting another phase II study in patients who have HER2-positive AGC without measurable lesions (HERBIS-1B; UMIN000007941) to confirm the usefulness of this regimen in this subgroup.

In conclusion, although this was not a randomised controlled study, our results suggest that SP plus trastuzumab has a good toxicity profile and promising efficacy, justifying the further study of regimens that contain SP and trastuzumab.

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CONFLICT OF INTEREST

Y Kurokawa, H Imamura, Y Komatsu, Y Doki, and T Tsujinaka received speaker honoraria from Taiho Pharmaceutical. Y Komatsu and Y Doki received unrestricted research grant from Taiho Pharmaceutical. The remaining authors declare no conflict of interest.

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ORIGINAL ARTICLE

Three-year outcomes of a phase II study of adjuvant chemotherapy with S-1 plus docetaxel for stage III gastric cancer after curative D2 gastrectomy

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Abstract
Background We have previously reported the superior feasibility and safety of adjuvant S-1 plus docetaxel in patients with stage III gastric cancer during a prospective phase II study. We report 3-year follow-up data on patients enrolled in this study.
Patients and methods Fifty-three patients with histologically confirmed stage III gastric cancer who underwent gastrectomy with D2 lymphadenectomy were enrolled into this study. They received oral S-1 (80 mg/m^2/day) for 2 consecutive weeks and intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (one cycle). Treatment was initiated within 45 days after surgery and repeated for four cycles, followed by S-1 monotherapy (4 weeks on, 2 weeks off) until 1 year after surgery. Three-year overall survival (OS) and disease-free survival (DFS) were evaluated.
Results The OS rate at 3 years was 78.4 % [95 % confidence interval (CI), 67.9–90.6 %] and the DFS rate at 3 years was 66.2 % (95 % CI, 54.4–80.7 %). Subgroup analyses according to disease stage showed a 3-year OS and DFS rate of 85.7 % (95 % CI, 74.9–98.1 %) and 70.8 % (95 % CI, 57.1–87.8 %) for stage IIIA, and 62.5 % (95 % CI, 42.8–91.4 %) and 56.2 % (95 % CI, 36.5–86.7 %) for stage IIIB, respectively.
Conclusions On the basis of 3-year follow-up data, postoperative adjuvant therapy with S-1 plus docetaxel

On the behalf of the Osaka Gastrointestinal Cancer Chemotherapy Study Group.

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yielded promising OS and DFS in stage IIIA gastric cancer patients who had undergone D2 gastrectomy. We believe that this regimen is a candidate for future phase III trials studying the optimal adjuvant chemotherapy regimen for stage III gastric cancer.

Keywords Adjuvant chemotherapy · Docetaxel · Gastric cancer · Three-year survival · S-1

Introduction

Although several meta-analyses have suggested that adjuvant chemotherapy provides a survival benefit for gastric cancer [1–7], efficacy has been established for only a few treatments in large clinical trials. Postoperative radiotherapy with 5-FU plus leucovorin has become a standard adjuvant regimen in the US [8], and the perioperative triplet regimen of epirubicin, cisplatin, and 5-FU is standard in the UK [9]. In Japan, adjuvant chemotherapy with S-1 is the current standard of care after curative gastrectomy with D2 lymphadenectomy (D2 gastrectomy) for histologically confirmed stage II/III disease [10]. Recently, 5-year follow-up data have been reported [11]. The S-1 group had a 5-year overall survival (OS) rate of 71.7 %, compared with 61.1 % in the surgery-alone group, corresponding to a 33 % reduced risk of death [hazard ratio (HR), 0.669; 95 % confidence interval (CI), 0.540–0.828]. However, approximately 35 % of patients still develop recurrence despite adjuvant S-1, and subgroup analyses have suggested S-1 is less efficacious for stage IIIB gastric cancer (HR, 0.791; 95 % CI, 0.520–1.205), in contrast to a clear survival benefit of S-1 demonstrated for stage II and IIIA disease [11].

Several attempts have been made to improve the efficacy of adjuvant S-1 chemotherapy. For example, Takahari et al. [12] have evaluated the feasibility of three cycles of S-1 plus cisplatin with subsequent S-1 monotherapy until 1 year after surgery for stage III gastric cancer. We have previously demonstrated that four cycles of S-1 plus docetaxel followed by S-1 monotherapy up to 1 year after surgery is a feasible regimen with moderate toxicity when used as adjuvant chemotherapy in patients with stage III gastric cancer after curative D2 gastrectomy [13].

The aim of this study was to evaluate the efficacy of S-1 plus docetaxel adjuvant chemotherapy for stage III gastric cancer in terms of survival to determine if this regimen is a potential candidate for the next adjuvant phase III chemotherapy trial.

Patients and methods

This study was conducted in accordance with the international ethical recommendations stated in the Declaration of Helsinki. The protocol was approved by the institutional review and ethics board of each participating hospital and was registered in the University Hospital Medical Information Network (UMIN) database (ID 000000714). Written informed consent was obtained from all patients.

Eligibility

Eligibility criteria were as follows: histopathologically confirmed stage IIIA or IIIB gastric cancer; R0 resection (with no tumor cells at the margin) with D2 or more extensive lymph node dissection; no evidence of hepatic, peritoneal, or distant metastasis; no tumor cells on peritoneal lavage cytology; age 20–80 years; Eastern Cooperative Oncology Group performance status 0–1; no previous treatment for cancer except for initial gastric resection of the primary lesion; adequate organ function; absence of other severe medical conditions; and absence of synchronous or metachronous malignancies. Tumor stage classification and D classification were in accordance with the Japanese Classification of Gastric Carcinoma (second English edition) [14]. Patients were enrolled within 6 weeks after surgery by means of facsimile.

Treatment

Patients were given S-1 in a daily dose of 80, 100, or 120 mg in two divided doses based on body surface area for 2 consecutive weeks with intravenous docetaxel (40 mg/m^2) on day 1, repeated every 3 weeks (one cycle). The treatment was started within 45 days after surgery and repeated for four cycles. After four cycles of S-1 plus docetaxel, S-1 monotherapy (4 weeks on, 2 weeks off) was continued until 1 year after surgery. The criteria for dose reduction resulting from toxicity have been described elsewhere [13].

Follow-up

Patients underwent hematological tests and assessments of clinical symptoms at least once during each cycle of combination chemotherapy with S-1 plus docetaxel and at 6-week intervals during S-1 monotherapy. From the second year onward, all patients were followed up at least every 3 months. Relapse was confirmed by imaging studies, including ultrasonography, computed tomography, and gastrointestinal endoscopy. Patients underwent abdominal computed tomography at intervals of 6 months or less for the first 3 years after surgery, and at 1-year intervals thereafter until 5 years after surgery, and also received gastrointestinal endoscopy at 1-year intervals. All patients were followed up for at least 3 years from the date of

treatment initiation or until death. None was lost to follow-up.

Statistical analysis

The sample size was calculated with an expected feasibility rate of 75 % and a threshold feasibility rate of 50 % for four cycles of treatments with S-1 plus docetaxel based on a two-sided alpha level of 0.05 and statistical power of 90 %. The planned sample size was 50 patients, allowing for a 20 % dropout rate. OS and disease-free survival (DFS) for up to 3 years from the date of treatment initiation were estimated for all patients and analyzed according to disease stage. OS was defined as the time from the date of treatment initiation to the date of death from any cause or last follow-up. DFS was defined as the time from the date of treatment initiation to the date when recurrence or a second malignancy was confirmed, death from any cause, or last follow-up, whichever came first. The survival curves were estimated using the Kaplan–Meier method, and the 95 % CIs for survival rate were estimated using Greenwood's formula. All statistical analyses were done with S-plus version 8.1 J (Mathematical Systems).

Results

Patients

Between May 2007 and August 2008, 53 patients (42 men and 11 women) with a median age of 65 years (range, 43–78) were enrolled from 13 institutions. Based on the Japanese classification criteria, 35 patients (66.0 %) had stage IIIA disease and 16 patients (30.2 %) had stage IIIB disease. There was 1 patient with stage II (T1N2) and IV (positive tumor cells on peritoneal lavage cytology) disease each. Patient characteristics are listed in Table 1. Details of feasibility, safety, and reasons for treatment discontinuation were described previously [13]. In brief, the completion rate of the planned four cycles of S-1 plus docetaxel was 79.2 % (95 % CI, 65.9–89.2 %), whereas the completion rate of four cycles of S-1 plus docetaxel and subsequent S-1 monotherapy for 1 year was 64.2 % (95 % CI, 49.8–76.9 %). The relative dose intensity of S-1 and docetaxel for four cycles of chemotherapy were 79.6 % and 87.8 %, respectively.

Table 1 Patient characteristics

	Patients ($n = 53$)
Age (years), median (range)	65 (43–78)
Male:female	42:11
ECOG PS	
0	31
1	22
Pathological type	
Intestinal	24
Diffuse	29
Stage[a]	
II	1
IIIA	35
IIIB	16
IV	1
T stage[b]	
pT1	1
pT2	20
pT3	30
pT4	2
N stage[b]	
pN0	1
pN1	26
pN2	19
pN3	7
M stage[b]	
M0	52
M1	1
Stage[b]	
II	11
IIIA	24
IIIB	9
IV	9

ECOG PS Eastern Cooperative Oncology Group performance status

[a] Japanese classification

[b] TNM classification by the 6th edition

OS and DFS

Survival analyses were performed on 51 patients, excluding the 2 patients whose disease stage did not fulfill the inclusion criteria. Fifteen patients died, of whom 13 died of relapsed disease and 2 of other causes such as systemic infection and pulmonary emphysema. Thirty-three patients are alive without recurrence. In addition, 1 patient is alive with a second malignancy and 2 experienced recurrence. No treatment-related deaths occurred within 30 days after treatment completion. The 3-year OS and DFS rates for all eligible 51 patients were 78.4 % (95 % CI, 67.9–90.6 %) and 66.2 % (95 % CI, 54.4–80.7 %), respectively, as shown in Fig. 1a, b. Kaplan–Meier estimates of the 3-year OS and DFS are shown according to disease stage, with 3-year OS rates of 85.7 % (95 % CI, 74.9–98.1 %) and 62.5 % (95 % CI, 42.8–91.4 %) for stages IIIA and IIIB (Fig. 2a), respectively, and 3-year DFS rates of 70.8 % (95 % CI, 57.1–87.8 %) and 56.2 % (95 % CI, 36.5–86.7 %) for stages IIIA and IIIB (Fig. 2b), respectively.

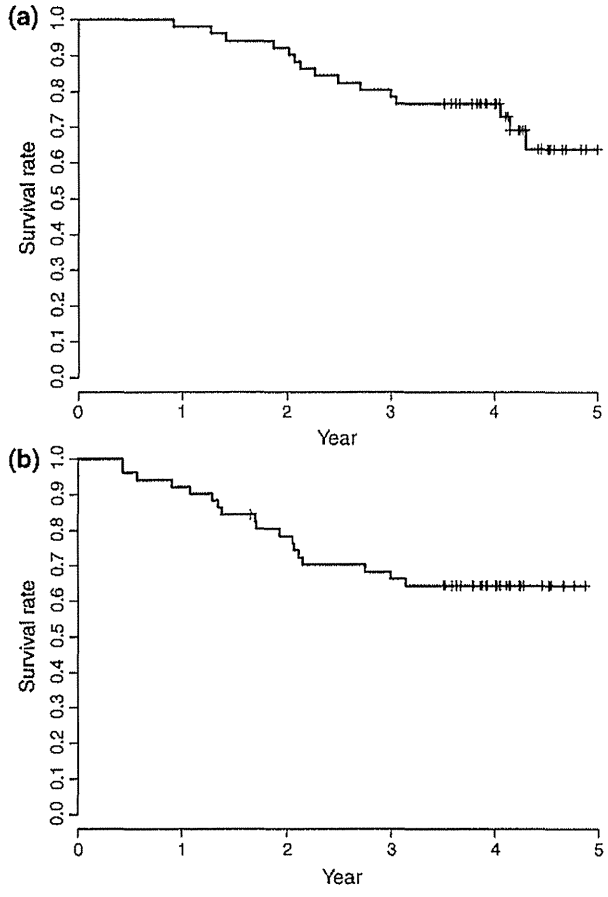

Fig. 1 **a** Kaplan–Meier estimates of 3-year overall survival for the eligible 51 patients. **b** Kaplan–Meier estimates of 3-year disease-free survival for the eligible 51 patients

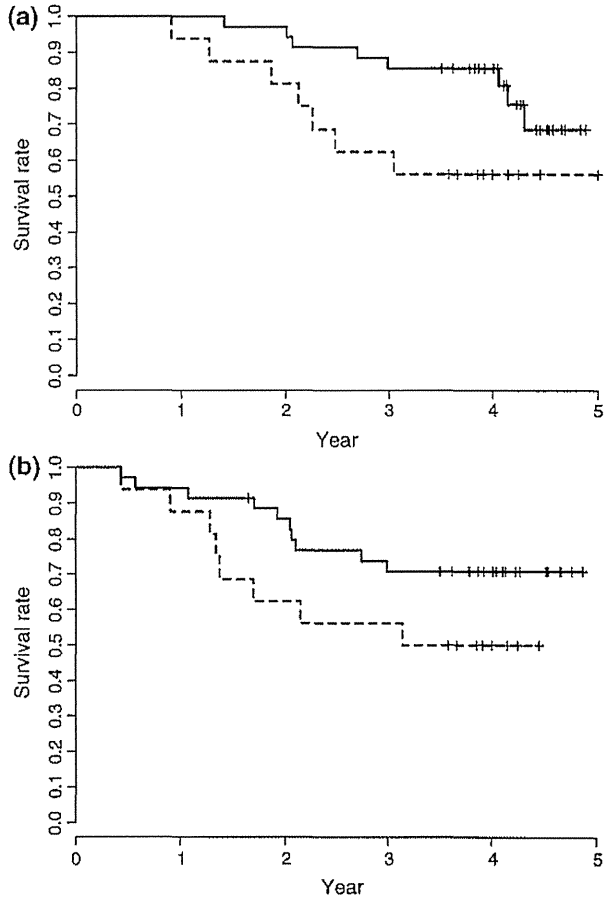

Fig. 2 **a** Kaplan–Meier estimates of 3-year overall survival for patients with stages IIIA and IIIB gastric cancer. *Solid line*, IIIA; *dotted line*, IIIB. **b** Kaplan–Meier estimates of 3-year disease-free survival for patients with stages IIIA and IIIB gastric cancer. *Solid line*, IIIA; *dotted line*, IIIB

Site of relapse

Fifteen patients had relapsed disease, involving nodal recurrence in 9 patients (1 cervical, 8 abdominal including paraaortic), hematogenous recurrence in 6 patients (5 liver, 1 spleen, 1 bone, 1 brain), and peritoneal dissemination in 4 patients.

Discussion

The mainstay of treatment for gastric cancer is surgery. However, in stage II and III disease, quite a few patients experience recurrence, even after curative resection. Adjuvant chemotherapy is used to prevent distant or local recurrence and improve survival. A recent meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group [7] has shown that postoperative adjuvant chemotherapy is associated with an 18 % risk reduction for both DFS (HR, 0.82; 95 % CI, 0.75–0.90) and OS (HR, 0.82; 95 % CI, 0.76–0.90) compared with surgery alone in patients with resectable gastric cancer. One year of S-1 monotherapy after D2 gastrectomy has been established as the standard of care in Japan for patients with stage II or III gastric cancer, with a 33 % reduced risk of death (HR, 0.669; 95 % CI, 0.540–0.828) [11], which was comparable to the mortality risk reduction of 26 % obtained by postoperative chemoradiotherapy in the US [8] or the 25 % obtained by perioperative triplet chemotherapy in the UK [9]. However, approximately one-third of patients still relapse despite adjuvant treatment with S-1, and subgroup analyses have shown insufficient efficacy of S-1 for stage IIIB disease (HR, 0.791; 95 % CI, 0.520–1.205) [11], suggesting there remains some room for improvement.

To improve the efficacy of adjuvant chemotherapy, another agent, docetaxel or cisplatin, both of which have shown effective cytotoxicity against advanced gastric cancer in several randomized controlled trials [15–17], was investigated in combination with S-1 for feasibility in the

adjuvant setting. Four cycles of S-1 plus docetaxel followed by S-1 monotherapy up to 1 year after curative D2 gastrectomy showed superior feasibility, with 79.2 % (95 % CI, 65.9–89.2) feasibility for the four planned cycles of S-1 plus docetaxel and good compliance with S-1 monotherapy at 12 months after surgery in 64.2 % of patients with stage III gastric cancer [13]. Treatment compliance at 12 months was compatible with results of the ACTS-GC trial that established 1 year of adjuvant S-1 monotherapy as the Japanese standard of care [10]. Similarly, three cycles of S-1 plus cisplatin subsequent to the first cycle of S-1 monotherapy was shown to be feasible in 81 % (95 % CI, 65–92) of patients with stage III gastric cancer [12].

Because of its high feasibility, the survival data for postoperative adjuvant chemotherapy with S-1 plus docetaxel followed by S-1 monotherapy for up to 1 year after surgery are eagerly awaited, and this regimen is now considered a potential candidate for an experimental arm in the next adjuvant phase III trial. The 3-year OS and DFS rates for the 51 eligible patients were 78.4 % (95 % CI, 67.9–90.6 %) and 66.2 % (95 % CI, 54.4–80.7 %), respectively (Fig. 1a, b). Kaplan–Meier estimates of the 3-year OS and DFS rates are shown according to disease stage, with 3-year OS rates of 85.7 % (95 % CI, 74.9–98.1 %) and 62.5 % (95 % CI, 42.8–91.4 %) for stages IIIA and IIIB (Fig. 2a), and 3-year DFS rates of 70.8 % (95 % CI, 57.1–87.8 %) and 56.2 % (95 % CI, 36.5–86.7 %) for stages IIIA and IIIB (Fig. 2b), respectively. In comparison, patients receiving adjuvant S-1 monotherapy in the ACTS-GC trial had 3-year OS rates of 77.4 % and 64.3 % for stages IIIA and IIIB, respectively, and 3-year relapse-free survival (RFS) rates of 69.1 % and 49.9 % for stages IIIA and IIIB, respectively (Table 2) [10, 18]. We also evaluated the stage-specific 3-year OS and RFS according to the sixth edition of the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours [19]. As shown in Table 2, for stage IIIA, 3-year OS and RFS rates according to UICC staging were 95.8 % (95 % CI, 88.2–100 %) and 79.2 % (95 % CI, 64.5–97.2 %) with S-1 plus docetaxel, and for S-1 monotherapy they were 77.8 % and 69.1 % in the ACTS-GC trial [11]. Similarly, for stage IIIB, 3-year OS and RFS rates were 55.6 % (95 % CI, 31.0–99.7 %) and 44.4 % (95 % CI, 21.4–92.3 %) with S-1 plus docetaxel, compared to 66.6 % and 44.8 % with S-1 monotherapy, in the ACTS-GC trial [11]. Based on these findings, adjuvant chemotherapy with four cycles of S-1 plus docetaxel followed by S-1 monotherapy until 1 year after surgery is expected to be more beneficial for UICC-TNM stage IIIA disease than S-1 monotherapy, but not for stage IIIB disease. However, the small sample size of each stage (UICC-TNM IIIA, $n = 24$; IIIB, $n = 9$) should be taken into careful consideration. Moreover, the recent CLASSIC trial [20] showed adjuvant chemotherapy with capecitabine plus oxaliplatin after D2 gastrectomy was associated with a survival benefit compared with surgery alone, with an improved 3-year DFS of 66 % (95 % CI, 57–75) and 61 % (95 % CI, 48–73) for UICC-TNM stage IIIA and IIIB disease, respectively; this suggests that adjuvant S-1 plus docetaxel may have a therapeutic benefit in stage IIIA gastric cancer. To further study its effect on stage IIIB disease, another phase II study of adjuvant S-1 with durable docetaxel for eight cycles is currently ongoing.

So far, 15 of 51 patients (29.4 %) have relapsed in this study, consisting of nodal recurrence in 17.6 %, hematogenous recurrence in 11.8 %, and peritoneal dissemination in 7.8 % of patients, compared with a total of 30.6 % of patients who developed recurrences with adjuvant S-1 monotherapy after D2 gastrectomy in the ACTS-GC trial with the peritoneum (14.6 %), hematogenous sites (11.5 %), and lymph nodes (5.7 %) as common sites of relapse [11]. In addition, S-1 plus docetaxel has recently shown superior survival to S-1 monotherapy in advanced gastric cancer patients with nonmeasurable lesions [17]. These findings suggest that postoperative adjuvant chemotherapy with S-1 plus docetaxel followed by S-1 monotherapy for up to 1 year after surgery is favorable for patients who are likely to relapse in the peritoneum, i.e., patients with linitis plastica.

In this study, 3-year OS as well as 3-year DFS was evaluated. An extremely strong correlation between DFS and OS was demonstrated by the GASTRIC group meta-analysis of 17 adjuvant trials after curative resection of gastric cancer [21]. In recent large clinical trials of adjuvant chemotherapy after curative D2 gastrectomy, 3-year RFS or 3-year DFS has been evaluated as surrogate measures of 5-year OS [10, 20], and it has been proven to become the primary endpoint for potentially curable gastric cancer, reconfirming the strong concordance of 3-year RFS with 5-year OS [11].

In conclusion, this 3-year follow-up study may suggest the efficacy of postoperative adjuvant chemotherapy with

Table 2 Comparison of results of the current study and the ACTS-GC trial

	3-year DFS/RFS (%)		3-year OS (%)	
	S-1 + DTX	ACTS-GC (S-1)	S-1 + DTX	ACTS-GC (S-1)
IIIA[a]	70.8	69.1	85.7	77.4
IIIB[a]	56.2	49.9	62.5	64.3
IIIA[b]	79.2	69.1	95.8	77.8
IIIB[b]	44.4	44.8	55.6	66.6

DFS disease-free survival, *RFS* relapse-free survival, *OS* overall survival, *DTX* docetaxel

[a] Japanese classification

[b] TNM classification by the 6th edition

four cycles of S-1 plus docetaxel followed by S-1 monotherapy for up to 1 year after D2 gastrectomy in patients with stage IIIA gastric cancer, while further studies for stage IIIB patients are needed. However, this study is a small-scale phase II study, not large enough to draw a definite conclusion on the survival benefit of combined adjuvant chemotherapy with S-1 plus docetaxel over S-1 monotherapy for stage III gastric cancer. Superior feasibility of this combined regimen in the adjuvant setting, and comparable OS and DFS in both regimens as shown in Table 2, warrant future phase III trial (S-1 plus docetaxel versus S-1 monotherapy) to identify the optimal adjuvant chemotherapy regimen for stage III gastric cancer.

Conflict of interest The authors declare no potential conflicts of interest.

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Anticancer Original Research Paper

Phase II study of S-1 monotherapy in patients over 75 years of age with advanced gastric cancer (OGSG0404)

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Background: S-1 + cisplatin (CDDP) is the standard treatment for advanced gastric cancer (AGC) in Japan and Korea. However, the usefulness of S-1 based chemotherapy for elderly patients is unclear. Therefore, we conducted a multicenter phase II study of S-1 monotherapy for AGC in elderly patients.
Materials and Methods: Chemotherapy-naïve patients aged over 75 years with AGC were enrolled. The starting dose of S-1 was determined on the basis of body surface area and modified according to the creatinine clearance value. S-1 was administered twice a day during a 4-week period followed by a 2-week rest period.
Results: Thirty-five patients were enrolled. The response rate (RR) was 14.3% and the median overall survival was 14.6 months. Grade 3 or more severe adverse events consisted of anaemia (3%), neutropaenia (3%), anorexia (3%), and fatigue (6%). There were no treatment-related deaths.
Conclusion: Our study indicates that S-1 monotherapy is safe and well tolerated in chemotherapy-naïve elderly patients with AGC, but exerts limited activity when given using a tailor-made dosing strategy based on renal function.

Keywords: S-1 monotherapy, Gastric cancer, Elderly, Phase II study

Introduction

In 2008, the estimated numbers of new gastric cancer cases and deaths from this disease worldwide were 0.99 million and 0.74 million, respectively. While these numbers are decreasing in developed countries, gastric cancer is still the fourth most common malignancy and the second leading cause of death following lung cancer. Sixty percent of gastric cancer cases worldwide occur in East Asia, including Japan, South Korea, and China.[1]

The proportion of elderly people in the Japanese population is increasing. According to a report by the Center for Cancer Control and Information Services of the National Cancer Center, the annual proportion of patients aged 75 years or older among the total number of patients who died of or were newly diagnosed with gastric cancer has been increasing.[2] Generally, as the functions of vital organs, particularly the kidneys and liver, decrease and complications develop in elderly patients, the toxicity of treatments can increase. Therefore, the risk–benefit analysis in relation to treatments for the elderly might be different from those for younger patients.

In many clinical phase III studies involving patients with advanced gastric cancer (AGC) in Japan the upper age limit for eligibility is 75 years. A similar age limit has been set in studies such as the SPIRITS study,[3] which evaluated S-1-based combination therapy with CDDP (SP, the standard therapy

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