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ORIGINAL ARTICLE

Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer

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Abstract
Purpose The use of trastuzumab, a monoclonal antibody targeting the HER2 protein, in combination with 5-fluorouracil/platinum-based chemotherapy improves survival in patients with HER2-positive advanced gastric cancer. In addition, TS-one (S-1)/platinum is also used as a standard of care in Asian countries. However, little is known about the combination of S-1/cisplatin chemotherapy and trastuzumab in patients with HER2-positive advanced gastric/gastroesophageal junction (GEJ) cancer.
Methods We conducted a single-arm, two-stage, open-label, multicenter phase II study. Trastuzumab was administered intravenously on day 1 of the first cycle at 8 mg/kg and 6 mg/kg on day 1 of subsequent cycles. Cisplatin was administered intravenously at 60 mg/m^2 on day 1 of each cycle after trastuzumab. S-1 was administered orally [based on body surface area (BSA)] twice a day for 14 days in a 3-weekly cycle. Patients with BSA of <1.25 received a total of 80 mg of S-1, those with BSA ≥1.5 received 120 mg, and the remaining received 100 mg daily in two divided doses.
Results All evaluable patients experienced tumor reduction during the trial. The primary end point (overall survival rate) was 59.3 %, with a clinical benefit rate of 66.7 %. Median progression-free survival was 7.4 months; 62.6 % patients were free from disease progression at 6 months. Median overall survival was 14.6 months, and the median time to treatment failure was 6.0 months.
Conclusion The combination of trastuzumab with S-1 and cisplatin demonstrated good activity, was generally well tolerated, and is a feasible treatment option in the first-line treatment of HER2-positive advanced gastric/GEJ cancers.

Keywords Gastric cancer · HER2 · Trastuzumab · HER2-positive gastric · Gastroesophageal junction (GEJ) cancers · TS-one (S-1) · Cisplatin

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Introduction

Gastric cancer is usually diagnosed at an advanced stage. First-line chemotherapy in advanced gastric cancer improves survival and quality of life; furthermore, combination chemotherapy is superior to single-agent chemotherapy [1–7]. HER2 is a key driver of tumorigenesis in gastric cancer [8]. The percentage of gastric cancers demonstrating HER2 overexpression ranges from 6 to 23 % [9–13]. HER2 overexpression is determined by either immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH) [12]. There is a high concordance between IHC and FISH HER2 results from both primary and metastatic sites [12, 14–18].

Trastuzumab is a recombinant monoclonal antibody targeting the extracellular domain of the HER2 protein. Bang et al. [19] showed that the addition of trastuzumab to cisplatin and capecitabine/5-fluorouracil increased the overall survival of patients with advanced HER2-positive gastric/gastroesophageal junction (GEJ) cancers, compared with chemotherapy alone.

S-1 is a novel oral fluoropyrimidine derivative with high oral bioavailability, comprising tegafur, 5-chloro-2,4-dihydropyrimidine, and potassium oxonate [20, 21]. A study conducted in 2010 by Abe et al. [22] suggested that cisplatin combined with TS-one (S-1) may be used as an effective treatment for advanced gastric cancer. Furthermore, studies have also shown that S-1 potentially reduced toxicities compared with 5-fluorouracil [23–25].

In addition, a Japanese phase III trial showed that the combination of S-1 and cisplatin was superior to S-1 alone in advanced gastric cancer [26]. Another phase III trial in non-Asians also studied the combination of cisplatin with either S-1 or infusional fluorouracil. Overall survival was similar, but S-1 was associated with an improved safety profile [27]. These trials showed that the combination of cisplatin and S-1 is a standard chemotherapy for upfront treatment of advanced gastric cancer [26, 28–31].

However, little is known about the combination of S-1/cisplatin chemotherapy and trastuzumab in patients with HER2-positive advanced gastric/GEJ cancer. Hence, the aim of our study was to conduct a single-arm, multicenter phase II study to demonstrate the safety and efficacy of the combination of trastuzumab with S-1 and cisplatin in patients with HER2-positive advanced gastric/GEJ cancers.

Methods

Eligibility

Patients aged ≥21 years with histologically/cytologically confirmed HER2-positive gastric or GEJ cancers were enrolled. HER2 positivity was defined as HER2 IHC 3+, or HER2 IHC2+/FISH positive. A FISH copy number value >2.2 was deemed positive. Post hoc exploratory analysis showed that patients who had IHC 3+ or IHC2+/FISH-positive gastric cancer derived the most benefit. If the patient's gastric tumor was in situ, obtaining tumor tissue endoscopically was mandatory. If the primary tumor had been resected, collection of further tissue samples was optional.

Patients were required to have measurable disease, European Cooperative Oncology Group (ECOG) performance status ≤2, and life expectancy ≥3 months. They had to be able to consume oral drugs, have normal organ and marrow function, and have a left ventricular ejection fraction (LVEF) of ≥50 %. Normal organ and hematological function were defined as hemoglobin ≥ 8.0 g/dL, leukocytes ≥ 3000/mcL, absolute neutrophil count ≥ 1500/mcL, platelets ≥ 100,000/mcL, total bilirubin ≤ 1.5 times upper limit of normal (ULN), aspartate transaminase (AST)/alanine aminotransferase (ALT)/alkaline phosphatase (ALP) ≤3 times ULN, and creatinine within normal institutional limits/creatinine clearance (using Cockcroft-Gault formula) ≥60 mL/min. In the presence of liver metastasis, AST, ALT, and ALP ≤ 5 times ULN were acceptable.

Patients with prior adjuvant chemotherapy/radiotherapy >180 days before enrollment were eligible, but prior systemic treatment for metastatic disease or any prior use of S-1, cisplatin, or trastuzumab was disallowed. Those with brain metastasis, radiotherapy in the preceding 4 weeks, or any prior malignancy (except basal cell carcinoma and preinvasive cervical cancer) diagnosed within the last 5 years were ineligible.

Also excluded were patients with serious complications/uncontrolled intercurrent illness that limited compliance with study requirements, those on other investigational agents, human immunodeficiency virus-positive patients, pregnant or lactating patients, and those with reproductive potential not amenable to implementing adequate contraceptive measures. Patients could not have active gastrointestinal bleeding requiring repeated transfusions.

Approval was obtained from the institutional review board of participating centers, and written consent was obtained from all patients.

Study design and sample size

We conducted a single-arm, two-stage, open-label, multicenter phase II study. Based on a sample size of 25 patients, the study was designed to distinguish a favorable overall response rate (ORR) of 55 % from a null rate of 30 % at 5 % significance level and 80 % power. Assuming an approximate 20 % loss to follow-up, the target size for enrollment was 30 patients.

Nine patients were used to evaluate the feasibility of the regimen in the first stage of the trial. An interim analysis based on these patients was performed, the regimen was deemed feasible, and the trial proceeded with second-stage patient accrual.

To speed up accrual, the trial changed from a single-center trial in the first stage to a multicenter trial with four recruitment sites in the second stage. Thirty patients were recruited in total, received trial stipulated treatment drugs, and were included in analysis.

Treatment plan

Chemotherapy was administered in a 3-weekly cycle. Trastuzumab was given intravenously at 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg on day 1 of subsequent cycles. Cisplatin 60 mg/m^2 was intravenously administered on day 1 of each cycle after trastuzumab. Hydration and antiemetic medication prior to and following cisplatin administration were administered according to institutional practice.

S-1 was administered orally twice a day for 14 days, followed by a rest period of 7 days. The initial dose of S-1 was determined based on body surface area (BSA). Patients with BSA < 1.25 received a total of 80 mg of S-1, those with BSA ≥ 1.5 received 120 mg, while all others received 100 mg daily in two divided doses.

Study treatment was continued until disease progression, unacceptable adverse events (AE), treatment delay of more than 3 weeks as a result of an AE, withdrawal of consent, or investigator's decision. Cisplatin could be discontinued after six cycles at investigator's discretion.

Dose reduction was permitted level by level with the lowest dose of S-1 and cisplatin set to 80 mg/day and 40 mg/m^2, respectively. Dose escalation was not permitted. Dose reductions were sequential for toxicity; cisplatin was reduced to 50 mg/m^2 and subsequently to 40 mg/m^2. S-1 dose was reduced by 20 mg/day for each dose reduction.

Cardiac assessment by MUGA Scan/2D-Echocardiography was performed prior to enrollment and every 3 months subsequently. Trastuzumab could be interrupted/discontinued for infusional reactions. Trastuzumab was withheld for at least 4 weeks and LVEF reassessed if there was a >16 % absolute decrease from baseline value or if it fell below the institution's normal limits and was at least a 10 % absolute decrease from pre-treatment value. Trastuzumab could be resumed if LVEF returned to normal limits and the absolute decrease from baseline was <15 % within 4–8 weeks. Trastuzumab was permanently discontinued if there was persistent (>8 weeks) LVEF decline or if its administration had to be suspended on more than three occasions for cardiomyopathy.

Evaluations

The primary end point was overall response rate (ORR). Secondary end points included progression-free survival (PFS), overall survival (OS), time to treatment failure (TTF), clinical benefit rate (CBR), duration of response (DR), and safety of the treatment regimen. Response and progression were evaluated using RECIST version 1.0 [25].

Patients were evaluated every 6 weeks with computed tomography/magnetic resonance imaging scans. Confirmatory scans were obtained at least 4 weeks following initial documentation of objective response. Patients who ended study treatment without progressive disease (PD) were followed for tumor response every 6 weeks from the end of study until PD or the initiation of any post-study anti-tumor therapy, whichever was earlier. All patients

Table 1 Patients' demographics and baseline clinical characteristics

	No.	%
Total	30	100
Age at histological diagnosis (years)		
Median	61.9	
Range	43.5–79.8	
Sex		
Female	8	26.7
Male	22	73.3
Ethnic group		
Chinese	17	56.7
Japanese	7	23.3
Korean	6	20.0
Primary tumor site		
Stomach	29	96.7
Gastricesophageal junction	1	3.3
Previous resection of primary tumor		
No	27	90.0
Yes	3	10.0
Histology type		
Intestinal	18	60.0
Diffused	1	3.3
Mixed	2	6.7
Not applicable	6	20.0
Not done	3	10.0
HER2 status		
IHC3+	22	73.3
IHC2+ and FISH+	8	26.7
Metastatic sites		
Liver	15	50.0
Lymph node	23	76.7
Lung	5	16.7
Peritoneum	7	23.3
Bone	2	6.7
Others	9	30.0
ECOG performance status		
0	15	50.0
1	15	50.0
Weight, kg		
Median	57.8	
Range	37.4–75.5	

HER2 human epidermal growth factor receptor 2; *IHC* immunohistochemistry; *FISH* fluorescence in situ hybridisation; *ECOG* Eastern Cooperative Oncology Group

Table 2 Relative dose intensities of trastuzumab, cisplatin, and S-1

	Mean RDI (%)	Median RDI (%)
Trastuzumab	99.80	100.00
Cisplatin	93.99	100.00
1st 6 cycles	93.97	100.00
S-1	89.82	100.00

RDI = actual total dose/planned dose (%) until discontinuation of drugs

Trastuzumab = 6 mg/kg per 3 weeks × treatment period (1st course: 8 mg/kg)

Cisplatin 60 mg/m^2 per 3 weeks × treatment period

S-1: 80 or 100 or 120 mg × 14 days per 3 weeks × treatment period

were followed up for 24 months after the last patient had initiated study treatment or until death, whichever occurred first. Survival status was assessed every 24 weeks over the phone from the end of study treatment.

OS was defined as time from registration to date of death. PFS was defined as time from registration until objective tumor progression or death from any cause, whichever occurred first. TTF was a composite end point measuring time from registration until treatment discontinuation. DR was defined as time from first assessment of CR (complete response) or PR (partial response) until the first date of PD or death within 60 days of the last tumor assessment or registration, whichever occurred first. Toxicities were graded according to the NCI CTCAE version 3.0.

Statistical analysis

All patients who received study-mandated treatment were included in the safety and efficacy analysis. Response rates were also assessed among evaluable patients, defined as those with measurable disease, had received ≥1 cycle of therapy, and had their disease re-evaluated.

Descriptive statistics were used to summarize patient demographics, baseline clinical characteristics, treatment modifications, and toxicities. Relative dose intensity (RDI) of each drug was estimated as the proportion of actual total dose to planned total dose received by patient until drug discontinuation. ORR and CBR were estimated using exact method [26]. Each survival distribution was estimated using Kaplan–Meier method. Exploratory association analysis of end points with demographics and clinical characteristics was assessed based on odds ratios for categorical outcomes and hazard ratios for survival outcomes. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

Between April 2010 and April 2013, a total of 30 patients were recruited, of whom three discontinued treatment.

Of the 30 recruited patients, one discontinued treatment during cycle 1 due to serious infusion reaction to

Table 3 Overall response rate based on RECIST version 1.0 and clinical benefit rate

	Among evaluable patients		Among all patients	
	No	%	No.	%
Total	27	100.0	30	100.0
Best overall response (BOR)				
Complete response (CR)	1	3.7	1	3.3
Partial response (PR)	15	55.6	15	50.0
Stable disease (SD)	6	22.2	6	20.0
Progressive disease (PD)	5	18.5	5	16.7
Not evaluable/not done[a]	0	–	3	10.0
Overall response rate (ORR)				
No. of patients with BOR = CR/PR	16		16	
ORR (95 % CI)	59.3 (38.8–77.6)	53.3 (34.3–71.7)		
Clinical benefit rate (CBR)				
No. of patients with BOR = CR/PR or SD over 24 weeks[@]	18		18	
CBR (95 % CI)			60.0 (40.6–77.3)	

CI confidence interval

[a] These patients discontinued treatment before first tumor re-evaluation in cycle 2: One passed away due to progressive disease before end of cycle 2, another had serious infusion reaction to trastuzumab in cycle 1, and the third refused treatment after trastuzumab infusion in cycle 1

trastuzumab, one refused treatment in cycle 1 after trastuzumab infusion, and another demised before the end of cycle 2 from treatment-related neutropenic sepsis. All three patients did not have their disease re-evaluated on treatment discontinuation. Twenty-four patients discontinued treatment as of September 30, 2013; reasons for discontinuation are listed in "Appendix 1."

Median age at diagnosis was 61.9 years (range 43.5–79.8 years) (Table 1). Majority were males (73 %), had primary tumor in the stomach (97 %), and had no prior resection of primary tumor (90 %). All had good performance status (ECOG 0 or 1). Majority (73 %) of patients' HER2 status was based on IHC3+. Sixty percent were histologically diagnosed with intestinal-type gastric cancer, and most were metastatic (87 %).

Treatment compliance

Four patients required dose reduction, 18 dose delay, and two dose omission of trastuzumab ("Appendix 2"). Most dose delays were hematology related. For cisplatin, 13 patients required dose reduction, 22 dose delay, and 19 dose omission. For S-1, 14 patients required dose reduction, 20 dose delay, and five dose omission.

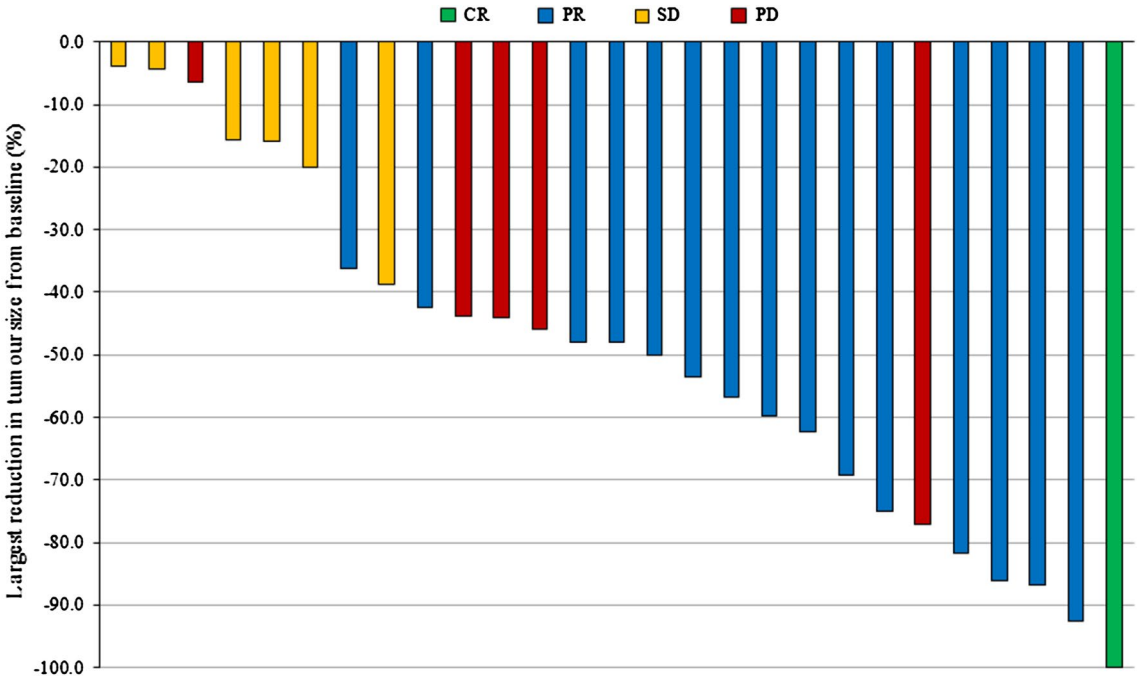

Fig. 1 Waterfall plot (among evaluable patients)

Table 4 Progression-free survival, overall survival, time to treatment failure, and duration of response estimates

	No. of events/patients	Median of distribution, months (95 % CI)	6-month rate, % (95 % CI)
Follow-up duration, months			
Median (range)		8.5 (0.1–26.8)	
Among all patients			
Progression-free survival	21/30	7.4 (5.5–11.0)	62.6 (41.5–77.9)
Overall survival	12/30	14.6 (9.7–26.8)	93.1 (75.1–98.2)
Time to treatment failure	24/30	6.0 (4.8–7.6)	47.3 (28.3–64.1)
Among patients whose best response is CR or PR			
Duration of response	11/16	7.3 (4.1–11.1)	55.6 (26.4–77.2)

CI confidence interval; *CR* complete response; *PR* partial response

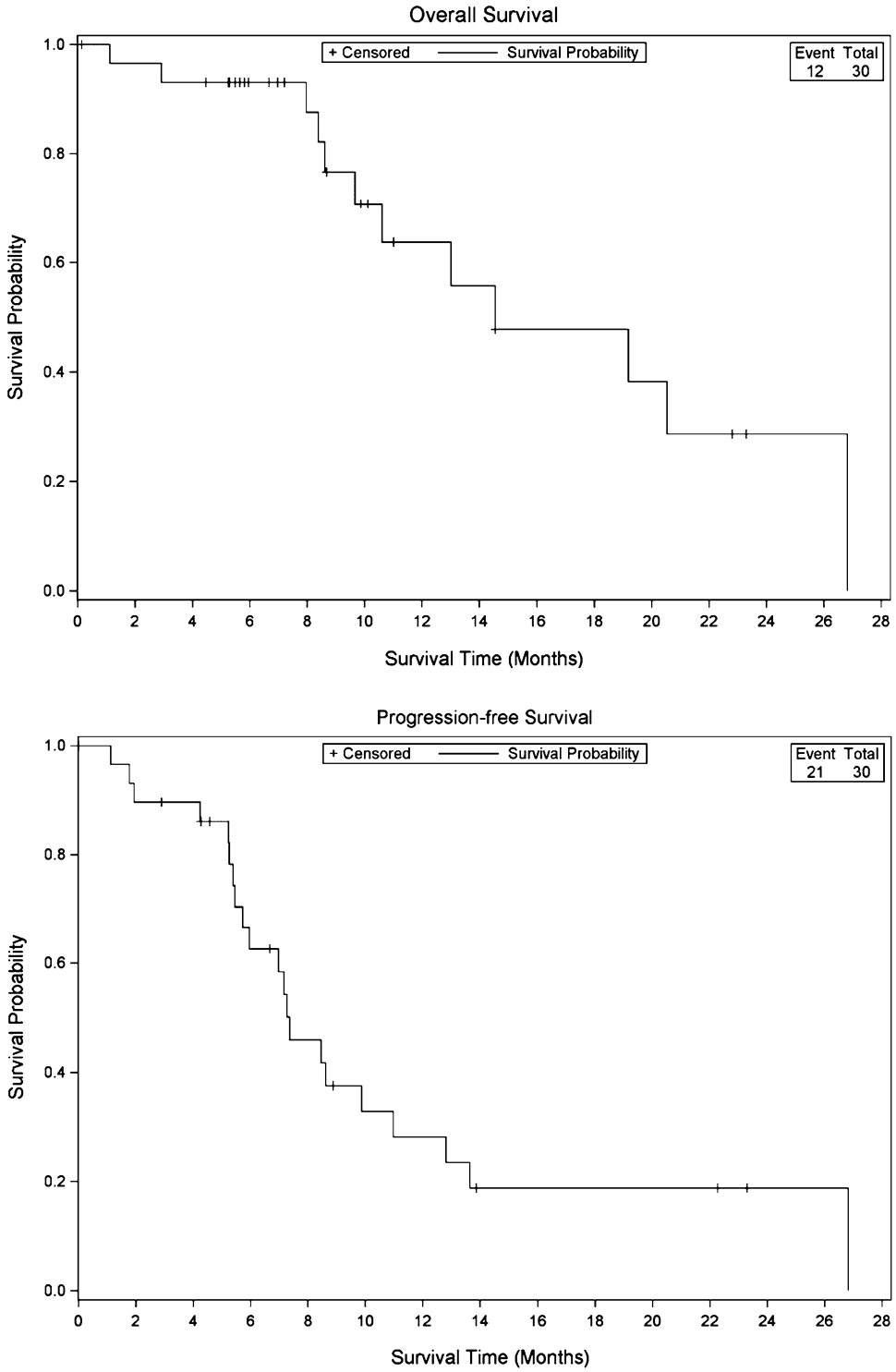

Fig. 2 Overall survival and progression-free survival curves

Relative dose intensities were 99.8 % for trastuzumab, 94.0 % for cisplatin, and 89.8 % for S-1 (Table 2). Half of the patients received the full dose for each drug.

Efficacy

Intention to treat analysis of the 30 patients showed one CR and 15 PR (Table 3). The ORR was 53.3 % (95 % CI

Table 5 Adverse events ($n = 30$)

	Total (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade ¾ (%)
Anemia	4 (13.3)	1	3	0	0	0 (–)
Leukopenia	5 (16.7)	0	3	2	0	2 (6.7)
Neutropenia	10 (33.3)	0	3	6	1	7 (23.3)
Febrile neutropenia	1 (3.3)	0	0	1	0	1 (3.3)
Thrombocytopenia	2 (6.7)	0	0	2	0	2 (6.7)
Hyperbilirubinemia	1 (3.3)	0	0	0	1	1 (3.3)
Left ventricular systolic dysfunction	1 (3.3)	1	0	0	0	0 (–)
Conjunctivitis	1 (3.3)	1	0	0	0	0 (–)
Teary eyes	2 (6.7)	2	0	0	0	0 (–)
Upper GI hemorrhage	1 (3.3)	0	0	1	0	1 (3.3)
Abdominal pain/cramp	3 (10.0)	1	2	0	0	0 (–)
Bloating/distention	3 (10.0)	1	1	1	0	1 (3.3)
Constipation	4 (13.3)	3	1	0	0	0 (–)
Diarrhea	14 (46.7)	9	0	5	0	5 (16.7)
Dyspepsia	1 (3.3)	1	0	0	0	0 (–)
Dysphagia	1 (3.3)	1	0	0	0	0 (–)
Epigastric discomfort	3 (10.0)	1	2	0	0	0(–)
Esophagitis	1 (3.3)	0	1	0	0	0 (–)
Mucositis/stomatitis	9 (30.0)	4	1	4	0	4 (13.3)
Nausea	14 (46.7)	12	1	1	0	1 (3.3)
Vomiting	5 (16.7)	3	2	0	0	0 (–)
Dysgeusia	3 (10.0)	2	1	0	0	0 (–)
Hiccup	3 (10.0)	3	0	0	0	0 (–)
Dry mouth	1 (3.3)	1	0	0	0	0 (–)
Fever (non-neutropenic)	2 (6.7)	0	2	0	0	0 (–)
Fatigue/lethargy	16 (53.3)	10	5	1	0	1 (3.3)
Edema	6 (20.0)	5	1	0	0	0 (–)
Infusion reaction	3 (10.0)	0	3	0	0	0 (–)
Hypoalbuminemia	1 (3.3)	0	0	1	0	1 (3.3)
Paronychia	1 (3.3)	1	0	0	0	0 (–)
LVEF drop	4 (13.3)	3	1	0	0	0 (–)
ALT/SGPT elevation	3 (10.0)	3	0	0	0	0 (–)
AST/SGOT elevation	3 (10.0)	3	0	0	0	0 (–)
Creatinine increased	2 (6.7)	2	0	0	0	0 (–)
Headache	2 (6.7)	2	0	0	0	0 (–)
Peripheral sensory neuropathy	1 (3.3)	1	0	0	0	0 (–)

ALT alanine transaminase; *SGPT* serum glutamic–pyruvic transaminase; *AST* aspartate aminotransferase; *SGOT* serum glutamic–oxaloacetic transaminase

34.3–71.7 %). Two additional patients had SD, leading to a CBR of 60.0 % (95 % CI 40.6–77.3 %). The ORR and CBR among the 27 evaluable patients were 59.3 % (95 % CI 38.8–77.6 %) and 66.7 % (95 % CI 46.0–83.5 %), respectively. All evaluable patients experienced tumor reduction during the trial (Fig. 1).

With a median follow-up duration of 8.5 months, the median PFS was 7.4 months (95 % CI 5.5–11.0 months) with 62.6 % of patients free from disease progression at the 6-month mark (Table 4). Eighteen patients were still alive at the time of analysis. Median OS was 14.6 months (Fig. 2), and median TTF was 6 months (95 % CI 4.8–7.6 months). Among the 16 patients who responded to the treatment, the median DR was 7.3 months.

None of the demographics and baseline clinical characteristics was significantly associated with ORR, CBR, PFS, or OS, including tumor HER2 status, histology, or primary tumor site.

Table 6 Patients with cardiac adverse events or LVEF drops during treatment

	No.	%
Total	30	100.0
LVEF drops during treatment[a]		
≥50 %	0	–
<50 %	15	50.0
<50 % and by ≥10 %	6	20.0
Leading to treatment discontinuation	0	–

LVEF Left ventricular ejection fraction

[a] Compared with baseline, based on the worst decrease in LVEF during treatment (if any)

Toxicities

All patients had at least one AE or serious adverse event (SAE). The commonest non-SAEs (any grade) included fatigue/lethargy (16 patients; 53.3 %), anorexia (53.3 %), diarrhea (46.7 %), and nausea (46.7 %) (Table 5). Majority (70 %) had at least one incidence of grade 3/4 AE. Common grade 3/4 non-SAE included neutropenia (23.3 %), low absolute neutrophil count (20.0 %), and mucositis/stomatitis (13.3 %).

Two patients suffered cardiac AEs; none led to permanent treatment discontinuation/death (Table 6). Half of the patients experienced a decline in LVEF from baseline during treatment; none suffered a LVEF drop of ≥50 % from baseline. Of these 15 patients, nine had a drop in LVEF of <10 % from baseline, while the remaining six patients suffered a >10 % (but <50 %) LVEF drop from their baseline readings. There were no incidences of cardiac failure or cardiac toxicity-related deaths.

Six patients discontinued study drugs as a result of AE or at investigator's decision. A total of 30 SAEs were reported. Two of them were fatal—one deemed a study drug-related grade 5 toxicity, while the other developed electrolyte and sugar disturbances and turned hypotensive.

Discussion

In our multicenter phase II single-arm study, high efficacy was observed with an ORR of 53.3 % in all patients and close to 60 % in the 27 evaluable patients. CBR was 60.0 and 66.7 %, respectively. All evaluable patients experienced tumor shrinkage during the course of the trial. With a median follow-up duration of 8.5 months, the median PFS and OS were numerically comparable to that seen in the ToGA study. There did not appear to be any difference in outcome between those with HER2 IHC 3+ and those with IHC2 2+/FISH+ cancers.

Similar to our study, Kurokawa et al. [31] reported a phase II Japanese trial combining trastuzumab with cisplatin and S-1 in HER2-positive advanced gastric cancers. They reported a response rate of 68 % (95 % CI 54–80 %) and a disease control rate of 94 % (95 % CI 84–99 %). Median OS, PFS, and TTF were estimated at 16, 7.8, and 5.7 months, respectively. Grade 3/4 AEs include neutropenia (36 %), anorexia (23 %), and anemia (15 %).

Chemotherapy was administered in a similar schedule in both studies, and both efficacy and toxicity end points were comparable. There was one death from neutropenic sepsis/infection attributable to treatment. Apart from that, the AEs and SAEs reported were expected, with no new safety concerns. There were no reported cardiac failure or cardiac toxicity-related deaths; of those who experienced LVEF drop, majority (60 %) had a <10 % drop from baseline.

In conclusion, the combination of trastuzumab with S-1 and cisplatin administered in a 3-weekly cycle demonstrated comparable efficacy to trastuzumab/cisplatin/capecitabine or fluorouracil and was generally well tolerated. This combination is an alternative option in the treatment of advanced HER2-positive gastric/GEJ cancer.

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Compliance with ethical standards

Conflict of interest Co-author, Dr. Choo Su-Pin, received a travel Grant from Taiho (which also provided the study Grant). Co-author, Dr. Yasuhide Yamada, received an honoraria and research Grant from Taiho.

Appendix 1

See Table 7.

Appendix 2

See Table 8.

Table 7 Listing of patients who have discontinued treatment

Patient ID	Discontinuation			No. of cycles administered before discontinuation			Second-line therapy
	At cycle	Reason	Remarks	TZ	Cisplatin	S-1	
1	8	PD	–	7	6	8	Docetaxel
2	8	Investigator's decision	SAE in November 10: hypotension, hypoglycemia, hypokalemia, neutropenia	8	6	8	Nil
3	8	PD	–	8	6	8	Docetaxel
4	2	Death	Cause of death = PD	2	2	2 (incomplete)	Nil
5	1	Investigator's decision	SAE in February 11: serious infusion reaction to trastuzumab	1	0	0	Trastuzumab, cisplatin and 5FU
6	9	PD	–	9	8	9	Nil
7	18	PD	–	18	6	18	Paclitaxel
8	7	AE/SAE	Persistent left femoral vein thrombosis before discontinuation	7	6	7	Gatsby trial (TDM-1)
9	15	AE/SAE	SAE in August 12: persistent diarrhea	15	6	15	Gatsby trial (TDM-1)
11	10	PD	–	10	6	10	Trastuzumab and paclitaxel
12	4	PD	–	4	4	4	Nil
13	8	PD	–	8	6	8	Nil
1001	6	RF	–	6	6	6	Discontinued in September 12, received trastuzumab, cisplatin and TS-one in December 12 and paclitaxel in May 13
1002	2	PD	–	2	2	2	S-1 (monotherapy)
1003	15	PD	–	15	11	15	Other new study drug
1004	11	PD	–	11	7	11	Other new study drug
1005	7	PD	–	7	7	7	Paclitaxel
2002	6	AE/SAE	SAE in May 13: upper GI hemorrhage G3	6	6	6	Nil (patient received radiotherapy)
2003	1	RF	–	1	0	0	Nil
2004	12	PD	–	12	12	12	Nil
2005	8	PD	–	8	8	8 (incomplete)	Nil
3001	4	AE/SAE	Persistent thrombocytopenia before treatment discontinuation	4	4	4	Nil
3002	8	PD	–	8	6	8 (incomplete)	Nil
3004	2	PD	–	2	2	2	Nil

TZ trastuzumab; *PD* progressive disease; *AE* adverse effects; *SAE* serious adverse effects; *RF* patient refusal to continue; *GI* gastrointestinal

Table 8 Listing of patients by drug modification of trastuzumab, cisplatin, and S-1

Patient ID	S-1							
	Reduction		Delay		Omission		Interruptions	
	# Cycles	Reasons	# Cycles	Reasons	# Cycles	Reasons	# Cycles	Reasons
1					1	Fatigue	2	DF
2							4	DF; took all daily tablets at same time
3					1	Infusion reaction to trastuzumab	1	AE
4	1	Took wrong dose					2	HP
5					1	Removed from study		
6	4	Hematology	1	Hematology			1	DF
7			1	Admitted for omentum repair operation			3	SU, HP, AE
8							2	AE, HP
9			3	Hematology (two cycles); overseas trip				
10			2	Fever; undeterminable CT scan results			1	HP
11			2	Hematology (two cycles); non-hematology (one cycle)			2	AE
12			2	Hematology			2	AE, PR
13							1	DF
1001	1	Hematology	1	Diarrhea				
1002	1	Diarrhea	1	Diarrhea				
1003	1	Diarrhea and stomatitis	3	Hematology				
1004			5	Hematology				
1005	1	Stomatitis	5	Hematology				
1006	1	Non-hematology	1	Non-hematology				
1007	2	Non-hematology	2	Non-hematology; Run errands			1	AE
2001	1	Lung infection	1	Lung infection			1	AE
2002	2	Non-hematology	1	Pulmonary thrombosis			1	AE
2003					1	Refused treatment	1	PR
2005			1	Hematology			1	AE
2006			3	Hematology				
3001	3	Hematology	2	Hematology				
3002	2	Hematology			1	PD on scan	2	nt dropped on floor and contaminated; PD on scan

Table 8 continued

Patient ID	S-1								
	Reduction		Delay		Omission		Interruptions		
	# Cycles	Reasons	# Cycles	Reasons	# Cycles	Reasons	# Cycles	Reasons	
3003	5	Hematology (3 cycles); non-hematology (one cycle); Diarrhea (one cycle)	5	Non-hematology (one cycle); diarrhea (one cycle); mucositis (one cycle); Shingles (one cycle); creatinine clearance (one cycle)			2	AE; CT scan in the morning	
3004	1	Non-hematology and urinary retention	1	Non-hematology and urinary retention			2	DF; PD on CT and MRI scan	

DF dose forgotten; *AE* treatment-related toxicity; *HP* hospitalization; *SU* surgical operation

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