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Efficacy and Safety of Trastuzumab in Combination with S-1 and Cisplatin Therapy for Japanese Patients with HER2-Positive Advanced Gastric Cancer: Retrospective Analysis

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The combinations of oral fluoropyrimidines and cisplatin such as capecitabine and cisplatin (XP) or S-1 and cisplatin (SP) are regarded as a standard therapy against unresectable, recurrent, or advanced gastric cancer (AGC). Especially, SP is the most common regimen against AGC in Japan. For patients with human epidermal growth factor receptor type 2 (HER2)-positive AGC, trastuzumab, a monoclonal antibody targeting HER2 antibody, is additionally used in combination. Although trastuzumab in combination with XP (trastuzumab-XP) have been widely accepted, the efficacy of trastuzumab in combination with SP (trastuzumab-SP) lacks sufficient verification. The aim of the present study is to validate the comparability of trastuzumab-SP to trastuzumab-XP. Patients with HER2-positive AGC were assigned to the trastuzumab-XP or trastuzumab-SP group. We then retrospectively compared the efficacy and safety between both groups. As a first-line chemotherapy, trastuzumab in combination with XP or SP was administered to 58 patients: 28 with trastuzumab-XP and 30 with trastuzumab-SP. In the trastuzumab-XP group, response rate (RR), disease control rate (DCR), median progression-free survival (mPFS), and median overall survival (mOS) were 39.3%, 89.3%, 7.9 months, and 20.0 months, respectively. In the trastuzumab-SP group, RR, DCR, mPFS and mOS were 50.0%, 86.7%, 6.9 months, and 16.7 months, respectively. No significant difference in efficacy was observed between both groups. Severe hand-foot syndrome was observed more frequently in the trastuzumab-XP group than in the trastuzumab-SP group (14.3% vs. 0%, $p = 0.05$). Trastuzumab in combination with SP is a potential first-line therapeutic option for patients with HER2-positive AGC.

Keywords: chemotherapy; gastric cancer; HER2; S-1; trastuzumab
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Introduction

Gastric cancer is the third most common cause of cancer-related deaths worldwide (Jemal et al. 2011; Global Burden of Disease Cancer Collaboration 2017). A significant fraction of patients with gastric cancer are diagnosed during the inoperable stages (Jou and Rajdev 2016). Moreover, although the efficacy of systemic therapy has been improving, the median survival time of unresectable, recurrent, or advanced gastric cancer (AGC) remains at 13.1-16.6 months (Yamada et al. 2015; Fujitani et al. 2016), suggesting that the prognosis for AGC is still poor. The global standard first-line chemotherapy for AGC is the combination of fluoropyrimidines and platinum such as fluorouracil plus cisplatin (FP) and capecitabine plus cisplatin (XP) combination therapies (Elimova et al. 2014). In Japan, S-1 plus cisplatin (SP) combination therapy is regarded as the standard first-line chemotherapy based on the SPIRITS and JCOG9912 trial (Koizumi et al. 2008; Boku et al. 2009). Capecitabine and S-1 are both oral fluoropyrimidines and are often compared (Su et al. 2014; Yamamoto et al. 2015).

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Trastuzumab is a monoclonal antibody that specifically binds to human epidermal growth factor receptor type 2 (HER2) (Hudis 2007). The ToGA trial, an international phase III study for 594 patients, demonstrated the effectiveness of adding trastuzumab to FP or XP combination therapies for HER2-positive AGC (Bang et al. 2010). Therefore, there is a consensus regarding the inclusion of trastuzumab in chemotherapy regimens for HER2-positive AGC. In contrast, the efficacy and safety of trastuzumab in combination with SP (trastuzumab-SP) therapy have been indicated in the HERBIS-1 trial, a Japanese domestic phase II study for 56 patients (Kurokawa et al. 2014). Based on the result of the HERBIS-1 trial, trastuzumab-SP therapy is considered as a potential treatment option for patients with HER2-positive AGC within Japanese guidelines (Japanese Gastric Cancer Association 2017). However, evidence of the efficacy and safety of trastuzumab-SP therapy remains insufficient. Given the low frequency of patients with HER2-positive gastric cancer (Lei et al. 2017), only a few clinical trials have targeted such type of cancer (Satoh et al. 2014; Thuss-Patience et al. 2017). Therefore, the present multicenter retrospective study compares treatment outcomes between trastuzumab in combination with XP (trastuzumab-XP) and trastuzumab-SP therapies in Japanese patients with HER2-positive AGC to validate the comparability of the two regimens.

Patients and Methods

Patients

From March 2011 to January 2016, patients with HER2-positive AGC at the Department of Medical Oncology of Tohoku University Hospital, Osaki Citizen Hospital, and Ishinomaki Red Cross Hospital were identified. The criterion of HER2 positive is defined as immunohistochemistry (IHC) 3+ or IHC 2+ and fluorescence in situ hybridization (FISH)-positive. Thereafter, a retrospective review of their medical records was conducted. Those who received trastuzumab-XP or trastuzumab-SP therapy as first-line chemotherapy were assigned to the trastuzumab-XP or trastuzumab-SP group, respectively. This study was approved by the Ethics Committee of the Faculty of Medicine, Tohoku University School of Medicine.

Treatment

Capecitabine (1,000 mg/m^2, twice a day, days 1-14, every 3 weeks) and S-1 (40 mg/m^2, twice a day, days 1-14, every 3 weeks) were administered in the trastuzumab-XP and trastuzumab-SP groups, respectively. On day 1 of each cycle (every 3 weeks), 80 and 60 mg/m^2 of cisplatin were administered intravenously in the trastuzumab-XP and trastuzumab-SP groups, respectively. In both groups, trastuzumab was also administered intravenously on day 1 of each cycle (every 3 weeks) at 8 and 6 mg/kg during the first and second or later courses, respectively. These procedures were in accordance with the ToGA and HERBIS-1 trials. Dose modifications were done at the discretion of the attending physicians depending on the patient's general condition and adverse events.

Evaluation and statistical analysis

Objective responses were evaluated according to Response Criteria in Solid Tumors version 1.1 (Eisenhauer et al. 2009). The response rate (RR) was defined as the rate of patients who achieved a complete or partial response, while the disease control rate (DCR) was defined as the rate of those who achieved a complete response, a partial response, or a stable disease. Progression-free survival (PFS) was defined as the period from day 1 of first-line chemotherapy until disease progression or death, whereas overall survival (OS) was defined as the period from day 1 of first-line chemotherapy until death. All toxicities were reviewed based on medical records and evaluated according to the Common Terminology Criteria for Adverse Events, version 4.0 (Tobinai et al. 1993). General conditions of the patients were assessed using the Eastern Cooperative Oncology Group Performance Status (Oken et al. 1982).

RR, DCR and toxicities were analyzed using two-sided Fisher's exact test. PFS and OS curves were constructed using the Kaplan-Meier method, while differences between the curves of the two subgroups were compared using the log-rank test. Hazard ratios for the trastuzumab-XP group versus trastuzumab-SP group were also calculated. All statistical analyses were performed using JMP Pro® 12 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

We identified 87 patients with HER2-positive AGC (Table 1). Those who had received trastuzumab-XP or trastuzumab-SP therapy as first-line chemotherapy were assigned to the trastuzumab-XP (n = 28) or trastuzumab-SP (n = 30) group, respectively. A total of 15, 8, and 6 cases had been treated with fluoropyrimidines alone, capecitabine plus oxaliplatin combination therapy, and other therapeutic drugs, respectively.

Baseline characteristics of the trastuzumab-XP and trastuzumab-SP groups are shown in Table 2. The median age was 68.5 and 63.5 years in the trastuzumab-XP and trastuzumab-SP groups, respectively. Notably, the trastuzumab-XP group had a significantly higher median age than the trastuzumab-SP group (*Wilcoxon rank sum test*, p = 0.03). No significant differences in other factors were observed between both groups.

Efficacy

The best overall responses of both groups are shown in Table 3. RR and DCR of all subjects included in the present study was 44.8% and 87.9%, respectively. Moreover, RR and DCR in the trastuzumab-XP or trastuzumab-SP groups were 39.3% and 89.3% or 50.0% and 86.7%, respectively. No significant differences in RR and DCR were observed between both groups.

Kaplan-Meier curves for PFS are shown in Fig. 1. The median PFS was 7.4 months (95% confidence interval [CI]: 6.3-10.2 months) in all subjects included in the present study. Furthermore, the median PFS in the trastuzumab-XP and trastuzumab-SP groups was 7.9 months (95% CI: 5.6-11.8 months) and 6.9 months (95% CI: 5.2-10.2 months), respectively. No significant difference was observed between both groups (p = 0.35).

Kaplan-Meier curves for OS are shown in Fig. 2. The

Table 1. All patients with HER2-positive inoperable advanced or recurrent gastric cancer.

	All		Tohoku University Hospital		Osaki Citizen Hospital		Ishinomaki Red Cross Hospital	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Total	87		23	(26.4)	39	(44.8)	25	(28.7)
Median Age	67		61		68		73	
Range	38-86		38-77		50-85		50-86	
Sex								
Male	71	(81.6)	17	(73.9)	34	(87.2)	20	(80.0)
Female	16	(18.4)	6	(26.1)	5	(12.8)	5	(20.0)
First line chemotherapy (plus trastuzumab)								
S-1 and cisplatin	30	(34.5)	14	(60.9)	12	(30.8)	4	(16.0)
Capecitabine and cisplatin	28	(32.2)	6	(26.1)	12	(30.8)	10	(40.0)
Fluorouracil	1	(1.1)	0		1	(2.6)	0	
Fluorouracil and cisplatin	1	(1.1)	1	(4.3)				
Docetaxel, cisplatin and S-1	1	(1.1)	0		1	(2.6)	0	
Docetaxel	1	(1.1)	1	(4.3)				
Nanoparticle albumin-bound paclitaxel	1	(1.1)	0		1	(2.6)	0	
Paclitaxel	2	(2.3)	0		2	(5.1)	0	
S-1	11	(12.6)	1	(4.3)	5	(12.8)	5	(20.0)
Capecitabine	3	(3.4)	0		3	(7.7)	0	
Capecitabine and oxaliplatin	8	(9.2)	0		2	(5.1)	6	(24.0)

HER2, human epidermal growth factor receptor type 2.

Table 2. Baseline characteristics.

	Trastuzumab-XP group		Trastuzumab-SP group	
	n	(%)	*n*	(%)
Total	28		30	
Median Age	68.5*		63.5*	
	44-81		38-74	
Sex				
Male	25	(89.3)	26	(86.7)
Female	3	(10.7)	4	(13.3)
Performance Status				
0	10	(46.7)	14	(35.7)
1	16	(43.3)	13	(57.1)
2	2	(10.0)	3	(7.1)
Primary Site				
Gastroesophageal junction	5	(17.9)	7	(23.3)
Gastric	23	(82.1)	23	(76.7)
HER2 status				
IHC 3+	23	(82.1)	25	(83.3)
IHC 2+/FISH positive	4	(14.3)	5	(16.7)
Unknown	1	(3.6)	0	
Number of following regimens				
0	8	(28.6)	7	(23.3)
1	7	(25.0)	9	(30.0)
2 ≧	13	(46.4)	14	(46.7)

XP, Capecitabine plus cisplatin therapy; SP, S-1 plus cisplatin therapy; HER2, human epidermal growth factor receptor type 2; IHC, immunohistochemistry.
*$p < 0.05$.

median OS in all subjects included in the present study was 18.6 months (95% CI: 15.2-25.1 months). Moreover, the median OS in the trastuzumab-XP and trastuzumab-SP groups was 20.0 months (95% CI: 13.0-29.2 months) and 16.7 months (95% CI: 12.2-25.7 months), respectively. No significant difference was observed between both groups ($p = 0.28$).

Dose of cisplatin

Since the standard dose of cisplatin is different between trastuzumab-XP and trastuzumab-SP, we compared delivered dose intensity of cisplatin among both groups

Table 3. Best overall responses.

Best Response	All		Trastuzumab-XP group		Trastuzumab-SP group	
	n	(%)	*n*	(%)	*n*	(%)
Complete response	4	(6.9)	2	(7.1)	2	(6.7)
Partial response	22	(37.9)	9	(32.1)	13	(43.3)
Stable disease	25	(43.1)	14	(50.0)	11	(36.7)
Progressive disease	4	(6.9)	1	(3.6)	3	(10.0)
Not evaluated	3	(5.2)	2	(7.1)	1	(3.3)
Response rate	44.8%		39.3%		50.0%	
Disease control rate	87.9%		89.3%		86.7%	

XP, Capecitabine plus cisplatin therapy; SP, S-1 plus cisplatin therapy.

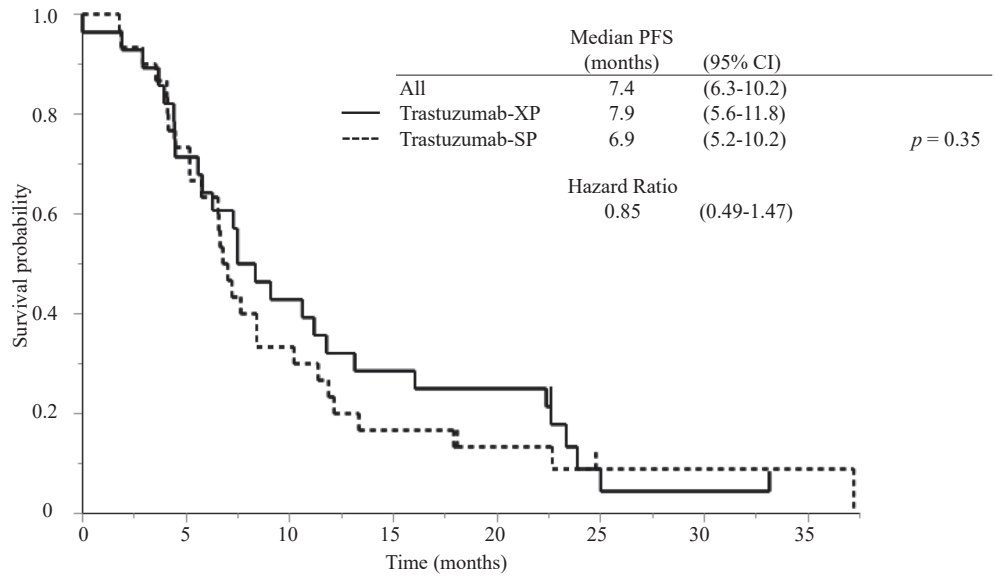

Fig. 1. Kaplan-Meier survival curves for progression-free survival.
Kaplan-Meier survival curves are shown for progression-free survival in the trastuzumab-XP (solid line) and trastuzumab-SP (dotted line) groups, respectively.

(Table 4). In the trastuzumab-XP group, the mean dose intensity of cisplatin was significantly higher than that in the trastuzumab-SP group (14.8 mg/m^2/week vs. 10.5 mg/m^2/week, $p = 0.01$). Although there was no significant difference in relative dose intensity of cisplatin among both groups, it was higher in the trastuzumab-XP group (55.6% vs. 52.6%, $p = 0.67$).

Adverse events

Hematological and nonhematological toxicities in the trastuzumab-XP and trastuzumab-SP groups are shown in Table 5. The frequencies of hematological toxicities were similar between both groups. The most frequent severe hematologic adverse event was neutropenia, with 28.6% and 26.7% in the trastuzumab-XP and trastuzumab-SP groups, respectively. Only two cases of febrile neutropenia were observed in the trastuzumab-SP group, whereas no case of grade 4 febrile neutropenia or death by febrile neutropenia was observed in both groups.

Grade 3 or 4 hand-foot syndrome was more frequently observed in the trastuzumab-XP group than in the trastuzumab-SP group (14.3% vs. 0%, $p = 0.05$). The frequencies of other nonhematological toxicities, such as anorexia, nausea, vomiting, diarrhea, and mucositis, did not significantly differ between both groups.

Discussion

Standard chemotherapy for AGC in Japan differs from that in western countries due to the history of clinical trials, medical insurance system, drug approval status, and so forth (Takashima et al. 2009). In Japan, SP therapy has been considered the standard primary chemotherapy based on results from the SPIRITS and JCOG 9912 trials (Koizumi et al. 2008; Boku et al. 2009). The ToGA trial was an international Phase III trial that showed the effectiveness of trastuzumab-containing chemotherapy for HER2-positive AGC (Bang et al. 2010). In the ToGA trial, FP or XP therapy was selected for combination with trastuzumab. Moreover, the HERBIS-1 trial, a domestic Phase II study in Japan, examined the efficacy and safety of trastu-

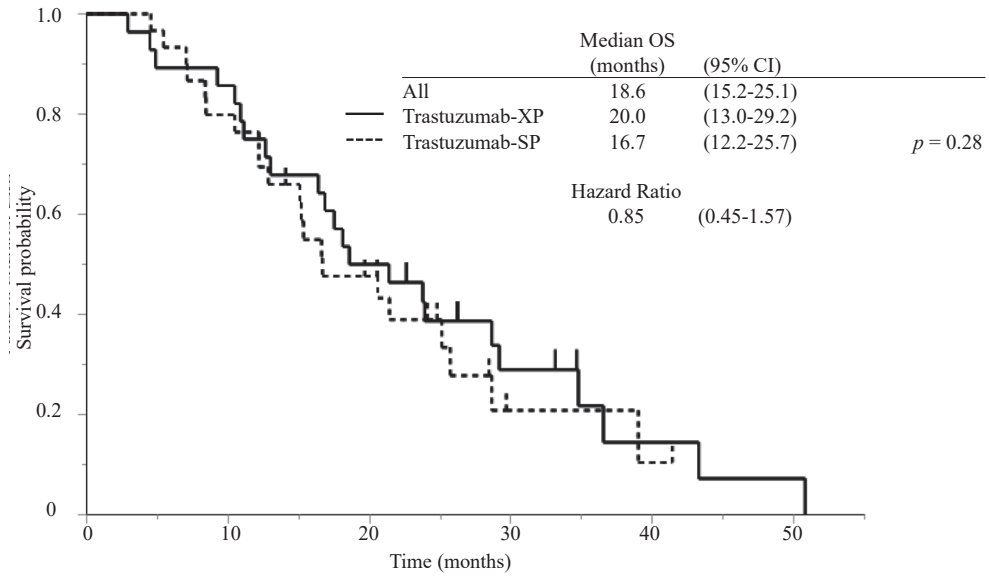

Fig. 2. Kaplan-Meier survival curves for overall survival.
Kaplan-Meier survival curves are shown for overall survival in the trastuzumab-XP (solid line) and trastuzumab-SP (dotted line) groups, respectively.

Table 4. Dose of cisplatin.

	Trastuzumab-XP group		Trastuzumab-SP group		*p* value
Standard dose intensity	26.7	mg/m2/week	20	mg/m2/week	
Delivered dose intensity	14.8 (95% CI: 11.6-18.1)	mg/m^2/week	10.5 (95% CI: 8.9-12.2)	mg/m^2/week	0.01
Relative dose intensity	55.6 (95% CI: 43.3-67.8)	%	52.6 (95% CI: 44.3-60.9)	%	0.67

XP, capecitabine plus cisplatin therapy; SP, S-1 plus cisplatin therapy; CI, confidence interval.

Table 5. Incidence rates of adverse events.

	Trastuzumab-XP group				Trastuzumab-SP group			
	All grades		Grade 3/4		All grades		Grade 3/4	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Any adverse event	26	(92.9)	17	(60.7)	28	(93.3)	17	(56.7)
Hematological								
Leukopaenia	12	(42.9)	0		8	(26.7)	2	(6.7)
Neutropenia	16	(57.1)	8	(28.6)	17	(56.7)	8	(26.7)
Anemia	21	(75.0)	6	(21.4)	26	(86.7)	7	(23.3)
Thrombocytopenia	14	(50.0)	1	(3.6)	16	(53.3)	2	(6.7)
Febrile neutropenia	0		0		2	(6.7)	2	(6.7)
Non-hematological								
Anorexia	20	(71.4)	4	(14.3)	14	(46.7)	3	(10.0)
Fatigue	12	(42.9)	4	(14.3)	13	(43.3)	3	(10.0)
Nausea	9	(32.1)	1	(3.6)	11	(36.7)	3	(10.0)
Vomiting	7	(25.0)	2	(7.1)	6	(20.0)	3	(10.0)
Diarrhoea	5	(17.9)	1	(3.6)	8	(26.7)	2	(6.7)
Constipation	2	(7.1)	1	(3.6)	4	(13.3)	0	
Mucositis	6	(21.4)	0		5	(16.7)	0	
Hand-foot syndrome	9	(32.1)	4	(14.3)*	7	(23.3)	0*	
Creatinine increased	8	(28.6)	1	(3.6)	10	(33.3)	0	
ALT increased	11	(39.3)	1	(3.6)	6	(20.0)	0	
Bilirubin increased	3	(10.7)	1	(3.6)	2	(6.7)	0	
Peripheral neuropathy	4	(14.3)	1	(3.6)	4	(13.3)	0	

XP, Capecitabine plus cisplatin therapy; SP, S-1 plus cisplatin therapy; ALT, Alanine transaminase.
*$p < 0.05$.

zumab-SP therapy (Kurokawa et al. 2014). Although the HERBIS-1 trial demonstrated the efficacy and safety of trastuzumab-SP therapy, the accumulation of evidence remains inadequate because of the paucity in the number of patients. The purpose of the present study was to validate the comparability of trastuzumab-SP to trastuzumab-XP against patients with HER2-positive AGC.

In the present study, no significant differences in RR, DCR, median PFS, and median OS were observed between the trastuzumab-XP and trastuzumab-SP groups. Moreover, RR, DCR, median PFS, and median OS were 47%, 79%, 6.7 months, and 13.8 months in the ToGA trial (trastuzumab-XP therapy) (Bang et al. 2010) and 68%, 94%, 7.8 months, and 16.0 months in the HERBIS-1 trial (trastuzumab-SP therapy) (Kurokawa et al. 2014). The clinical outcomes in the present study were similar to those in the HERBIS-1 and ToGA trials (Bang et al. 2010; Kurokawa et al. 2014), supporting the efficacy of trastuzumab-containing regimens in clinical practice. Moreover, our results suggest that clinical outcomes of trastuzumab-SP therapy are comparable with those of trastuzumab-XP therapy in clinical practice.

The results of the ToGA and HERBIS-1 trials seem to suggest that trastuzumab-SP therapy demonstrates more favorable therapeutic effects than trastuzumab-XP therapy (Bang et al. 2010; Kurokawa et al. 2014). This difference might have been caused by the difference in eligibility criteria for HER2 status in each trial. The ToGA trial included samples that scored 3+ on IHC or tested positive during FISH, whereas the HERBIS-1 trial included IHC 3+ or IHC 2+ and FISH-positive samples. Moreover, the median OS in the ToGA trial had extended to 16.0 months when only IHC 3+ or IHC 2+ and FISH-positive cases were analyzed. Furthermore, only 38% of patients in the ToGA trial received second-line chemotherapy. Although the HERBIS-1 trial did not show data for second-line chemotherapy, a majority of Japanese patients with AGC generally receive second-line or later chemotherapies (Miura et al. 2017). The difference in the ratio of second-line or later chemotherapies between the ToGA and HERBIS-1 trials may be attributed to the longer OS in the HERBIS-1 trial than that in the ToGA trial.

The present study showed no significant difference in PFS and OS between the trastuzumab-XP and trastuzumab-SP groups. However, PFS and OS tended to be longer in the trastuzumab-XP group than in the trastuzumab-SP group. One reason for this difference in survival time tendencies, especially PFS, between the trastuzumab-XP and trastuzumab-SP groups might be the treatment dose of cisplatin. The standard cisplatin dose for trastuzumab-XP therapy in the ToGA trial was 26.7 mg/m^2/week, whereas that for trastuzumab-SP therapy in the HERBIS-1 trial was 20 mg /m^2/week (Bang et al. 2010; Kurokawa et al. 2014). In the present study, the mean dose intensity of cisplatin was 14.8 mg/m^2/week (55.6% of standard dose) and 10.5 mg/m^2/week (52.6% of standard dose) in the trastuzumab-XP and trastuzumab-SP groups, respectively. The difference in relative dose intensities of cisplatin between both groups might have influenced survival times. The trastuzumab-XP group also tended to have longer OS than the trastuzumab-SP group. Since there was no significant difference in number of following regimens between both groups, this difference in OS may reflect the difference in PFS of first-line chemotherapy between both groups.

In the present study, grade 3 or 4 hand-foot syndrome, which is a typical side effect of capecitabine (Hofheinz et al. 2015), occurred more frequently in the trastuzumab-XP group than in the trastuzumab-SP group. This difference was similar to previous studies comparing capecitabine and S-1 (Lee et al. 2008; He et al. 2015). The frequency of severe hand-foot syndrome by capecitabine was somewhat higher in the present study than previously reports (Hofheinz et al. 2015). In the present study, as it was a retrospective study, there was no strict procedure for dosage and supportive care; however, since all hospitals participating in the present study had medical oncologists, they had properly treated hand-foot syndrome with urea-based cream, steroids and so on. Therefore, the reason why the frequency of severe hand-foot syndrome was high in the present study is unclear. Differences in patient background between clinical trials and clinical practice may have affected the outcome. Generally, patients participating in clinical trials are in very good general condition. Except for hand-foot syndrome, no significant difference in the other adverse events had been observed between both groups.

The limitations of the present study include its retrospective design and the small number of subjects. However, to the best of our knowledge, there have been no studies directly comparing clinical results between trastuzumab-SP and trastuzumab-XP therapies in patients with HER2-positive AGC thus far. Given the retrospective design of the present study, drawing a firm conclusion proved to be difficult. However, our results suggest that the efficacy and safety of trastuzumab-SP therapy are comparable with those of trastuzumab-XP therapy. Our present study supports the results of the HERBIS-1 trial wherein trastuzumab-SP therapy is considered a potential first-line therapeutic option for patients with HER2-positive AGC.

Conflict of Interest

The authors declare no conflict of interest.

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