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Original Article

Comparison of the Effect of Proton Pump Inhibitors on Capecitabine and S-1 in Gastric Cancer Treatment with Trastuzumab; A Multi-Institutional Analysis

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ABSTRACT

Introduction: The effect of proton pump inhibitors on capecitabine- and S-1-based treatment for human epidermal growth factor receptor 2 (HER2)-positive gastric cancer is unknown. Therefore, we compared the effect of proton pump inhibitors between capecitabine- and S-1-based treatments for HER2-positive gastric cancer.

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Methods: In a multi-institutional study, we retrospectively analyzed the effect of proton pump inhibitors on 155 HER2-positive advanced or recurrent gastric cancer patients who were treated with oral 5-fluorouracil (capecitabine or S-1) and trastuzumab. Capecitabine- and S-1-based treatments were compared in terms of the response rate and time to treatment failure, and the negative effects of proton pump inhibitors on the treatment response were evaluated. In this study, the primary endpoint was the response rate, and the secondary endpoint was time to treatment failure.

Results: There was no significant difference in the response rate between the capecitabine- and S-1-based treatments. However, in cases without proton pump inhibitor intake, the response rate significantly improved with capecitabine-based treatment rather than with S-1-based treatment ($P = 0.046$). Compared with the S-1-based treatment, the capecitabine-based treatment significantly prolonged the time to treatment failure ($P = 0.044$), including for patients with differentiated adenocarcinoma ($P = 0.035$).

Conclusions: For HER2-positive and differentiated gastric cancer, capecitabine-based treatment may be better than S-1-based treatment. Proton pump inhibitors might decrease capecitabine's effects and should be avoided to increase the response rate to capecitabine-based treatment.

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KEYWORDS: proton pump inhibitor, HER2-positive gastric cancer, capecitabine, S-1, trastuzumab

Introduction

According to the ToGA trial results,[1] trastuzumab was approved for human epidermal growth factor receptor 2 (HER2)-positive gastric cancer in March 2011. In some reports comparing the effects of capecitabine and S-1 for HER2-negative gastric cancer, no significant difference was observed in the survival time between capecitabine and S-1,[2–5] with, generally, the combination treatment of trastuzumab, oral 5-fluorouracil (5-FU) (capecitabine or S-1), and platinum drugs (cisplatin [CDDP] or oxaliplatin [l-OHP]) having been used as a first-line treatment for HER2-positive gastric cancer.[6] There was no prospective study comparing capecitabine-based treatment with S-1-based treatment for HER2-positive gastric cancer. A recent retrospective study on 87 patients with HER2-positive gastric cancer reported no significant difference in efficacy between capecitabine/CDDP/trastuzumab and S-1/CDDP/trastuzumab.[7]

Meanwhile, a subgroup analysis of the TRIO-013/LOGiC Randomized Clinical Trial for HER2-positive gastric cancer indicated that proton pump inhibitors (PPIs) decreased the effects of capecitabine.[8] With this multi-institutional, retrospective analysis aiming to assess PPIs' effect on capecitabine- and S-1-based treatments for HER2-positive gastric cancer, it would be valuable to assess PPIs' negative effects on capecitabine and S-1 treatment for HER2-positive gastric cancer.

Methods

Patients

Based on a review of medical records from eight hospitals (i.e., the Toho University Omori Medical Center, the University of Tokyo Hospital, The Jikei University Hospital, the NTT Medical Center Tokyo, the Showa University Hospital, the Japanese Red Cross Medical Center, the Toho University Ohashi Medical Center, and the National Hospital Organization Tokyo Medical Center) between March 2011 and December 2017, we retrospectively collected data from 155 cases that were treated with a combination of oral 5-FU (capecitabine or S-1) and trastuzumab.

Treatment

Seventy-one patients received capecitabine (1,000 mg/m^2, twice a day, on days 1-14, every three weeks) combined with trastuzumab (8 mg/kg in the first dose, 6 mg/kg after the second dose). Eighty-four patients received S-1 (40 mg/m^2, twice a day, on days 1-14, every three weeks) combined with trastuzumab. One hundred and sixteen patients (74.8%) received CDDP at a range 40-80 mg/m^2 for each cycle. Nineteen patients (12.3%) received l-OHP at a range of 80 to 130 mg/m^2 for each cycle. Twenty patients (12.9%) did not receive platinum agents. Seventy-eight patients did not received PPIs, and 77 patients received PPIs (Table 1). The PPIs were received in parallel with the oral 5-FU.

Table 1 Baseline characteristics in Patients

Variables		Capecitabine group (n = 71)	S-1 group (n = 84)	*P* value
Median age (range)		69 y.o. (35-87)	68 y.o. (39-89)	0.450[1)]
Gender	Male (n)	53	64	0.823[2)]
	Female (n)	18	20	
Pathology	Differentiated type	41	56	0.252[2)]
	Undifferentiated type	30	28	
HER2 Status	IHC 2+/FISH or DISH+	19	23	0.931[2)]
	IHC 3+	52	61	
Disease Status	Unresectable	41	57	0.193[2)]
	Recurrent	30	27	
M factor	Positive	47	72	0.004[2)]
	Negative	24	12	
First line chemotherapy (plus trastuzumab)	plus CDDP	47	69	0.001[2)]
	plus l-OHP	16	3	
	alone	8	12	
Acid suppression drugs	Without PPIs	33	45	0.378[2)]
	With PPIs	38	39	

1) Mann-Whitney's U test 2) Chi-squared test
HER2 = human epidermal growth factor receptor–related 2; FISH = fluorescence *in situ* hybridization; DISH = dual color in situ hybridization; IHC = immunohistochemistry; CDDP = cisplatin; l-OHP = oxaliplatin; PPIs = proton pump inhibitors

Evaluation of efficacy and statistical analysis

The patients were compared according to groups, based on the: 1) treatment received (capecitabine group [capecitabine/trastuzumab ± platinum agent] vs. S-1 group [S-1/trastuzumab ± platinum agent]); 2) use of PPIs (PPI group vs. non-PPI group); and 3) pathologic classification (differentiated type [tubular adenocarcinoma: tub1/tub2] vs. undifferentiated type [poorly differentiated adenocarcinoma; por, Signet-ring cell carcinoma; sig and other]). Treatment efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors Guideline.[9)]

Mann-Whitney *U*-test used to compare median age and response rate. Chi-squared test was used to compare categorical data such as gender, pathological type, HER2 status, disease status, M factor, platinum drugs, and PPIs. Kaplan-Meier survival curves were obtained based on the survival time from the initial date of treatment. The censoring date was December 31, 2018. Differences in survival time were evaluated using the log-rank test. Hazard ratios for the comparison of the capecitabine and the S-1 groups were calculated by Cox proportional hazards model.

All *P*-values were calculated using two-sided testing, and *P*-values <0.05 were considered statistically significant. All statistical analyses were performed with StatMate V for Win&Mac Hybrid (ATMS Co., Ltd., Tokyo, Japan).

Ethical approval

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, the Toho University (# A19017, #A16084).

Results

Patients' characteristics

We used 155 patients with HER2 positive gastric cancer in Table 1. The median age was 69 years (range 35-87) and 68 (range 39-89) years in the capecitabine group and the S-1 group, respectively. The number of patients for each pathologic type in the capecitabine group was 41 for differentiated type and 30 for undifferentiated type. The number of patients for each pathologic type was 56 for differentiated type and 28 for undifferentiated type in the S-1 group. There were 19 patients with HER2 2+/FISH or DISH positive tumors and 52 patients with HER2 3+ tumors in capecitabine group. There were 23 patients with HER2 2+/FISH or DISH positive tumors and 61 patients with HER2 3+ tumors in the S-1 group. The number of patients for disease status was 41 for unresectable cancer and 30 for recurrent cancer in the capecitabine group. The number of patients for disease status was 57 for unresectable cancer and 27 for recurrent cancer in the capecitabine

Table 2 Overall response rate and subgroup response rate

Overall response rate (n) %									
Treatment		(n)	CR (n) %	PR (n)	SD (n) %	PD (n) %	RR %	DCR%	*P* value
Capecitabine group		71	8.5 (6)	31.0 (22)	22.5 (16)	38.0 (27)	39.5	62	0.509[1)]
S-1 group		84	4.8 (4)	33.3 (28)	17.9 (15)	44.0 (37)	38.1	56	
Subgroup response rate (n) %									
Capecitabine group	without PPIs (n = 78)	33	15.1 (5)	36.4 (12)	21.2 (7)	27.3 (9)	51.5	72.7	0.046[1)]
S-1 group		45	6.7 (3)	28.9 (13)	13.3 (6)	51.1 (23)	35.6	48.9	
Capecitabine group	with PPIs (n = 77)	38	2.6 (1)	26.3 (10)	23.7 (9)	47.4 (18)	28.9	52.6	0.256[1)]
S-1 group		39	2.6 (1)	38.4 (15)	23.1 (9)	35.9 (14)	41.0	64.1	
Capecitabine group	in differentiated type (n = 97)	41	2.4 (1)	39.0 (16)	22.0 (9)	36.6 (15)	41.4	63.4	0.191[1)]
S-1 group		56	5.4 (3)	37.5 (21)	16.1 (9)	41.0 (23)	42.9	59.0	
Capecitabine group	in undifferentiated type (n = 58)	30	16.7 (5)	20.0 (6)	23.3 (7)	40.0 (12)	36.7	60.0	0.313[1)]
S-1 group		28	3.6 (1)	25.0 (7)	21.4 (6)	50.0 (14)	28.6	50.0	

1) Mann-Whitney's U test

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RR = response rate; DCR = disease control rate

Upper column: overall response rate between the capecitabine and S-1 groups

Middle column: subgroup response rate based on PPIs use and type of oral 5-FU

Lower column: subgroup response rate based on pathologic type and type of oral 5-FU

group. In the recurrent cases, the classification of total gastrectomy and partial gastrectomy was unknown. The number of patients for M factor was 47 for positive and 24 for negative in the capecitabine group. The number of patients for M factor was 72 for positive and 12 for negative in the S-1 group. Among the capecitabine group, trastuzumab was combined with capecitabine plus CDDP, capecitabine plus l-OHP, and capecitabine alone in 47, 16, and 8 cases, respectively. Among the S-1 group, trastuzumab was combined with S-1 plus CDDP, S-1 plus l-OHP, and S-1 alone in 69, 3, and 12 cases, respectively. There were 33 patients without PPIs and 38 patients with PPIs in the capecitabine group. There were 45 patients without PPIs and 39 patients with PPIs in S-1 group. There were no significant differences in age, gender, pathology, HER2 status, and acid suppression drugs between the capecitabine group and the S-1 group, however, there were significant differences in M factor and treatment (Table 1).

Response rate

As shown in Table 2, 8.5% of the capecitabine group had a complete response (CR), 31.0% had a partial response (PR), 22.5% had stable disease (SD), and 38.0% had progressive disease (PD); in the S-1 group, 4.8% had CR, 33.3% had PR, 17.9% had SD, and 44.0% had PD. There were no significant differences in the response rates between the capecitabine and S-1 groups ($P = 0.509$).

The response rates among the four groups, based on PPIs use and type of oral 5-FU, are shown in Table 2. Among the patients who did not receive PPIs, the CR, PR, SD, and PD were 15.1%, 36.4%, 21.2%, and 27.3%, respectively, in the capecitabine group and 6.7%, 28.9%, 13.3%, and 51.1%, respectively, in the S-1 group; there were significant differences in the response rates between the capecitabine and S-1 groups ($P = 0.046$). On the other hand, among the patients who received PPIs, there were no significant differences in response rates between the capecitabine and S-1 groups ($P = 0.256$).

The response rates among the four groups, based on pathologic type and type of oral 5-FU, are shown in Table 2. Among the patients who had the differentiated type, the CR, PR, SD, and PD were 2.4%, 39.0%, 22.0%, and 36.6%, respectively, in the capecitabine group and 5.4%, 37.5%, 16.1%, and 41.0%, respectively, in the S-1 group; there were no significant differences in the response rates between the capecitabine and S-1 groups ($P = 0.191$). Likewise, among the patients who had the undifferentiated type, there were no significant differences in the response rates between the capecitabine and S-1 groups ($P = 0.313$).

Time to treatment failure and Overall survival and Treatment discontinuation factor

The median TTF and overall survival time (OS) were five months (Fig. 1a) and 20 months (Fig. 1b), respectively. The treatment failure causes are shown in Fig. 1c. Treatment was discontinued because of PD in most patients (n

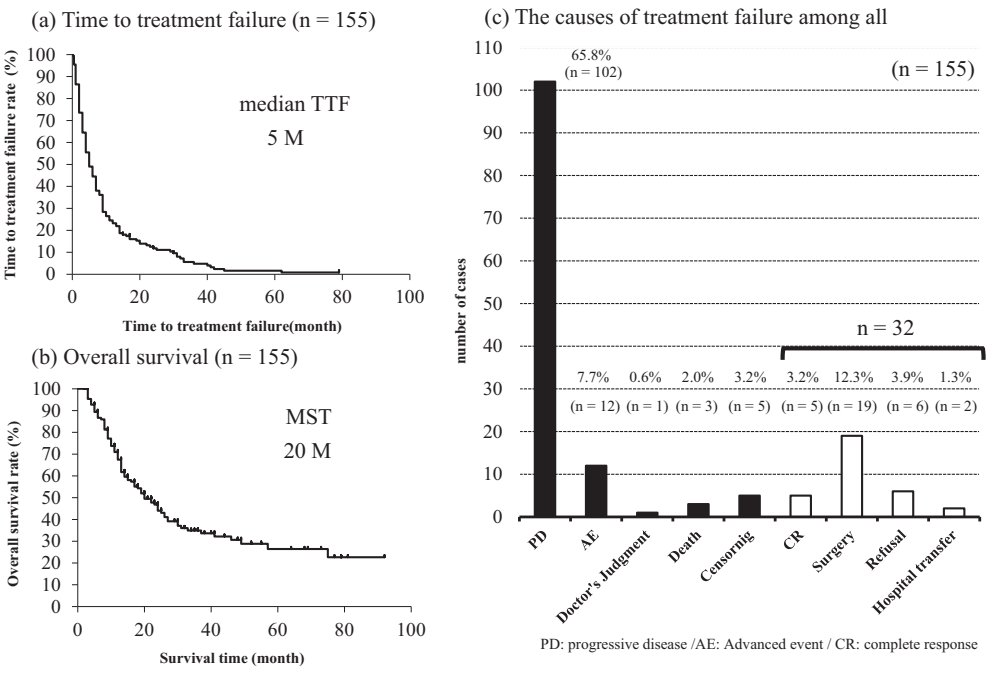

Fig. 1 Prognosis of the gastric cancer patients treated with Trastuzumab. (a) Time to treatment failure, (b) Overall survival, and (c) The causes of treatment failure among all patients (n = 155).

= 102); adverse events (n = 12); and other reasons (n = 32), such as CR (n = 5), surgery (n = 19), refusal (n = 6), and hospital transfer (n = 2). Of the five patients with CR, three were maintained in CR, but two eventually developed PD and died.

Comparison of time to treatment failure and overall survival between capecitabine and S-1

To investigate the prognosis associated with treatment risk, we focused on 123 cases, excluding those who had CR, underwent surgery, refused, and/or were transferred to another hospital (Fig. 2). The TTF was significantly longer in the capecitabine group than in the S-1 group (P = 0.044) (Fig. 2a). There was no significant difference in OS between the capecitabine and S-1 groups (P = 0.574) (Fig. 2b).

Time to treatment failure according to PPI treatment and pathologic type

As shown in Fig. 3, the TTF was similar between the capecitabine and S-1 groups among patients who did not receive PPIs (P = 0.113) and among those who received PPIs (P = 0.186). As shown in Fig. 4, The TTF was significantly longer in the capecitabine group than in the S-1 group (P = 0.035) in patients with the differentiated type, but it was similar between the capecitabine and S-1 groups (P = 0.596) in patients with the undifferentiated type.

Hazard ratios for the capecitabine and S-1 groups

In the subgroup analyses of TTF based on a univariate Cox proportional hazards model, none of the four groups (based on with/without PPIs or pathological type) showed statistically significant differences between the capecitabine group and the S-1 group. However, among patients who did not receive PPIs and/or those with a differentiated type, the hazard ratio for TTF was especially lower (0.65/0.62) in the capecitabine group than in the S-1 group (Fig. 5).

Discussion

In this multi-institutional study, we compared the effect of PPIs between capecitabine- and S-1-based treatments for HER2-positive gastric cancer. The response rates to capecitabine and S-1 significantly differed among patients who did not receive PPIs, while capecitabine, compared with S-1, significantly prolonged the TTF. Although the response rates to capecitabine and S-1 were similar, regardless of the pathological type, the TTF was significantly longer with capecitabine than with S-1 among patients with the differentiated type.

According to previous reports, PPIs resulted in worse progression-free survival (PFS), OS, and disease control rates in gastric cancer patients treated with capecitabine

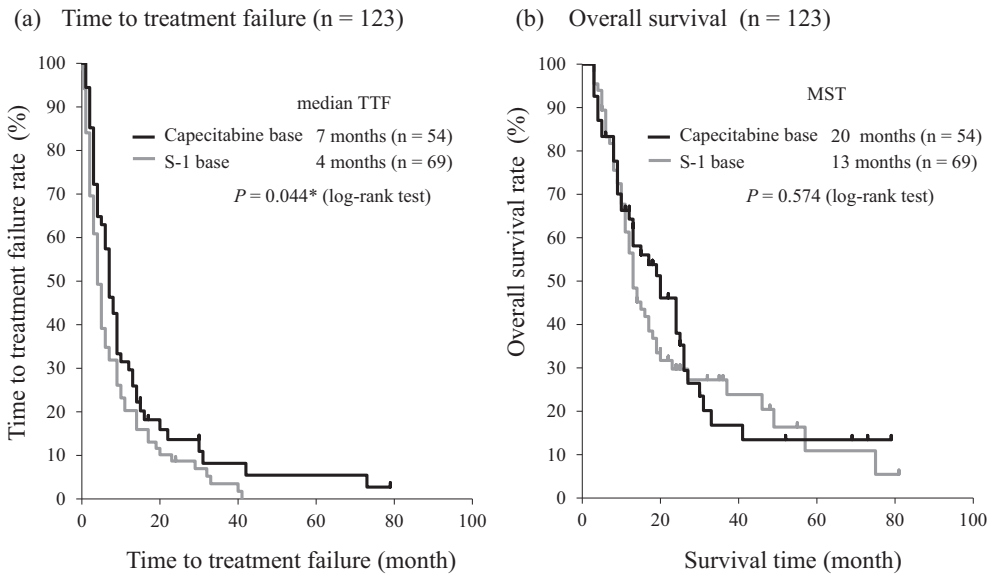

Fig. 2 Prognosis of the gastric cancer patients (n = 123) treated with Trastuzumab excluding complete response, surgery, refusal, and/or hospital transfer cases. (a) Time to treatment failure, (b) Overall survival.

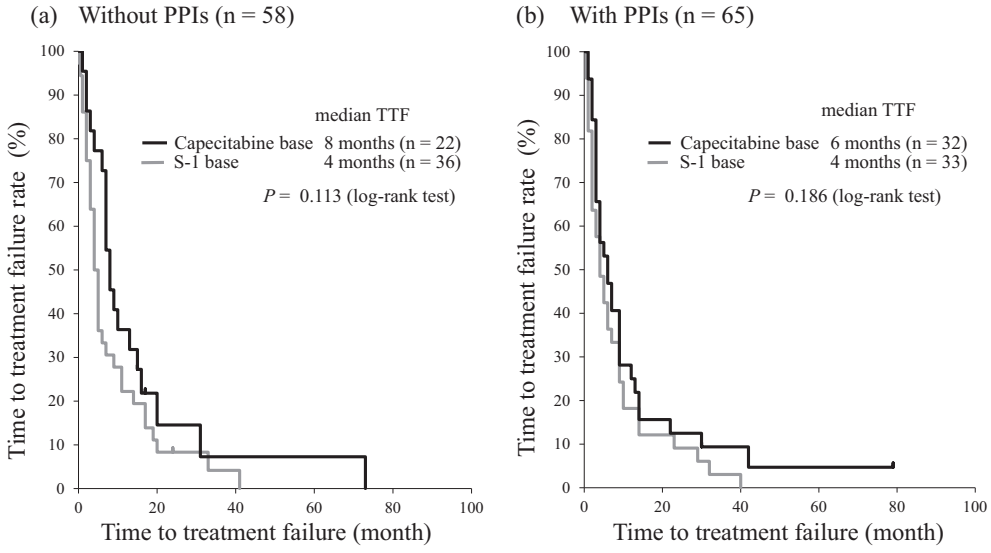

Fig. 3 Time to treatment failure of the gastric cancer patients (n = 123) treated with Trastuzumab excluding complete response, surgery, refusal, and/or hospital transfer cases. (a) The patients without PPIs treatment (n = 58), (b) The patients with PPIs treatment (n = 65).

and l-OHP[8] and worse relapse-free survival, and PFS rates in colorectal cancer patients treated with capecitabine.[10–12] Our results were consistent with those of previous reports, which showed PPIs' negative effects on the response rates to capecitabine. Moreover, concomitant administration of gastric acid suppressants, such as PPIs, with tyrosine kinase inhibitors appeared to decrease the efficacy of erlotinib, sunitinib, and pazopanib.[13–15] A randomized crossover pharmacokinetic study showed that cola intake (pH 2.5) led to a clinically relevant and statistically significant increase in erlotinib's bioavailability during PPI treatment, compared with the marginal effects of cola among patients who were not treated with PPIs.[16] Therefore, gastric pH might decrease capecitabine's bioavailability. On the other hand, similar to the previous report by Scheulen et al.,[17] our data confirmed that S-1

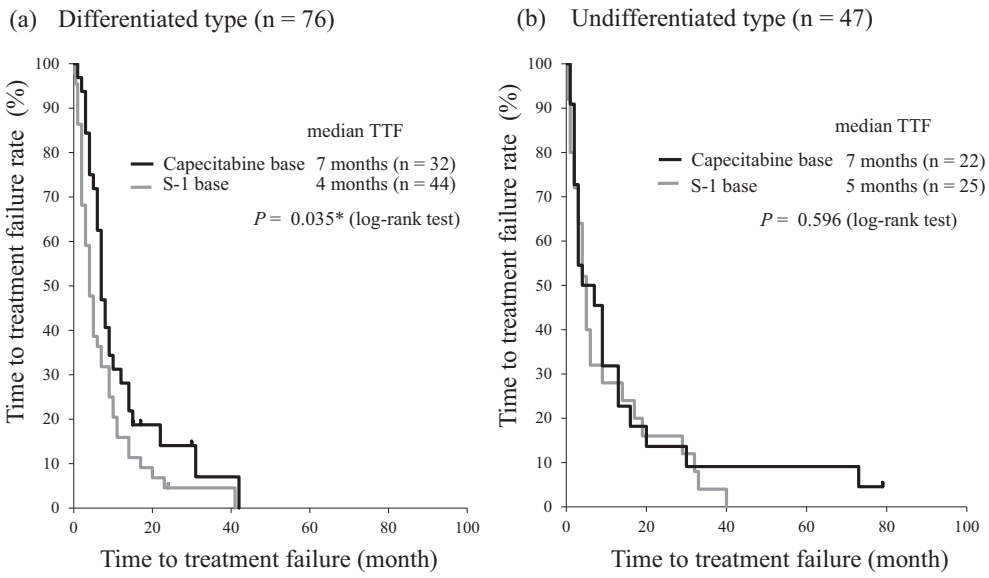

Fig. 4 Time to treatment failure of the gastric cancer patients (n = 123) treated with Trastuzumab excluding complete response, surgery, refusal and/or hospital transfer cases. (a) Differentiated type (n = 76), (b) Undifferentiated type (n = 47).

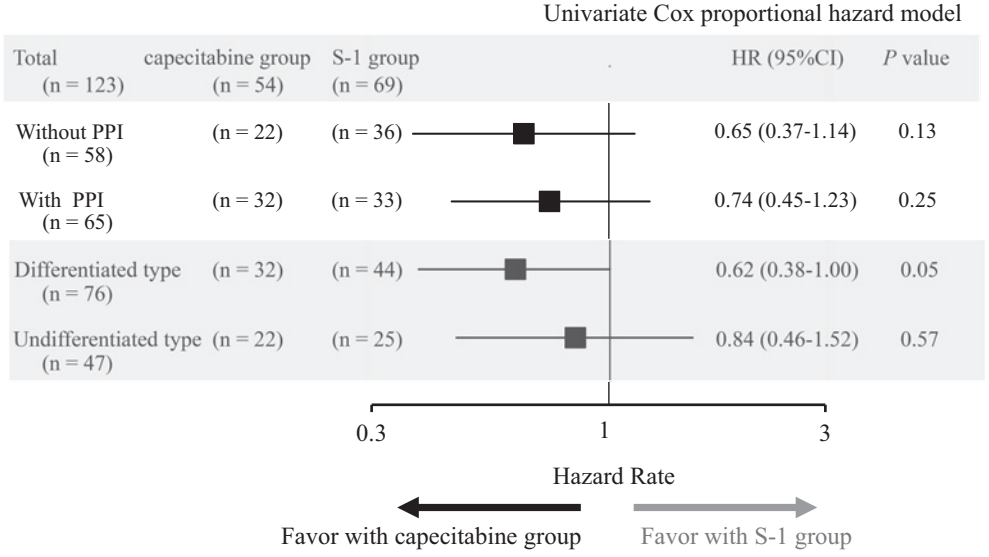

Fig. 5 Forest plot for subgroup univariate analyses of time to treatment failure (n = 123). Data are stratified HR (95% CI). HR = hazard ratio

bioavailability was not affected by PPIs. However, Kim et al.[18] reported that PPIs did not reduce the incidence of tumor bleeding from inoperable advanced gastric cancer patients, who are often treated with PPIs. In fact, half our present series used PPIs. Moreover, Chisaki et al.[19] reported that PPIs reduced the gastrointestinal toxicity caused by S-1 in gastric cancer. Taken together, the concomitant use of PPIs may be better with S-1, but not with capecitabine.

Capecitabine is converted to the active form of 5-FU by thymidine phosphorylase,[20] which was reportedly expressed more in differentiated adenocarcinomas than in undifferentiated adenocarcinomas.[21] Moreover, intestinal type, absence of peritoneal metastasis, and hepatic metastasis were identified as the significant independent factors related to HER2 positivity.[22] Capecitabine-based treatment has been suggested as an effective regimen for HER2-positive gastric cancer, as capecitabine is sensitive

in cells with relatively high thymidine phosphorylase activity.[23] Therefore, this hypothesis was confirmed in our present study. Among patients with differentiated type adenocarcinoma, capecitabine significantly prolonged the TTF, although, compared with S-1, it did not significantly increase the response rates.

The present study was multi-institutional; however, it was a retrospective study, so a limitation was that the clinical stage and treatment regimens were not accounted for in the subgroups. And this study is a retrospective study with too small a sample size to draw any meaningful conclusions. In addition, we could not analyze the relationship between surgical procedures and PPIs for recurrent gastric cancer. Recently, Wakatsuki reported that HER2 heterogeneity was a poor prognostic factor for HER2-positive gastric cancer.[24] However, we have not examined the HER2 heterogeneity of the patient's stomach cancer tissue.

In conclusion, for differentiated type gastric cancer treated with trastuzumab, capecitabine-based treatment may be better than S-1-based treatment. Because of the possibility of reduced effects of capecitabine, concomitant PPI use should be avoided.

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