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ORIGINAL ARTICLE

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

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

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

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Introduction

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

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

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

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

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

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

Patients and methods

Patient characteristics

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

Treatment

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

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

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

Plasma sampling and drug assay

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

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

Pharmacokinetic analyses

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

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

Results

Patient characteristics

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

Effect of trastuzumab and cisplatin on the pharmacokinetics of capecitabine

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

Table 1 Patient characteristics (mean ± SD)

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

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

Effect of trastuzumab and capecitabine on the pharmacokinetics of cisplatin

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

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

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

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

Table 3 Pharmacokinetic parameters for cisplatin (mean ± SD)

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

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

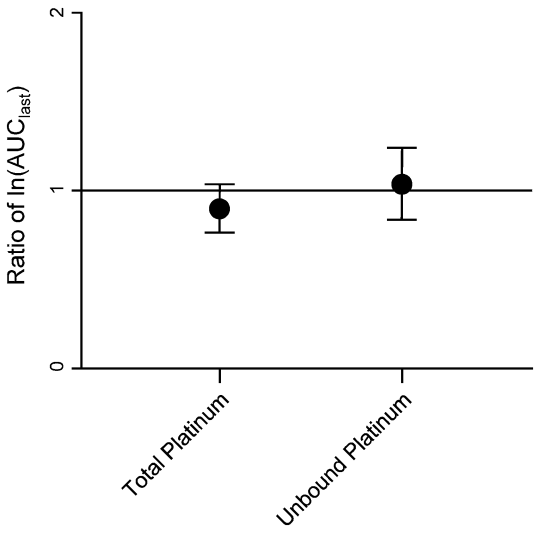

Fig. 1 The ratios (HXP arm/XP arm) of ln(AUC_{last}) for total and unbound platinum. *Error bars*, 90% CI

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

Pharmacokinetics of capecitabine and cisplatin: comparison with the literature

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

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

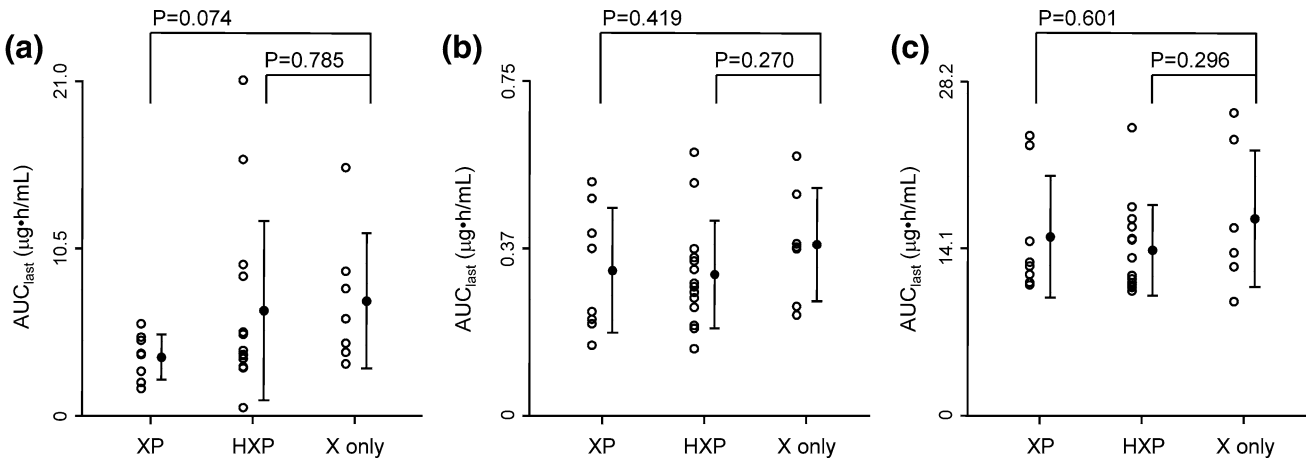

Fig. 2 Dose-normalized AUC_{last} for **a** capecitabine, **b** 5-FU, and **c** FBAL. Mean ± SD. *X*, capecitabine; *P*, cisplatin; *H*, trastuzumab. *P* values were calculated by Welch's test

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

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

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

Discussion

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

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

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

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

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

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

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

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

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