



Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer



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Abstract Background: Trastuzumab has been approved for use in combination with fluoropyrimidine plus cisplatin for the treatment of human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (AGC). Although capecitabine plus oxaliplatin (XELOX) is a standard first-line regimen for AGC, combination trastuzumab plus XELOX has not been studied.

Methods: Patients with metastatic or unresectable HER2-positive AGC were diagnosed by either HER2 immunohistochemistry (IHC) 3+ or IHC 2+/*in-situ* hybridisation (FISH)+ received intravenous trastuzumab (8 mg/m² for first cycle and 6 mg/m² for subsequent cycles on day 1) plus oral capecitabine (1000 mg/m² twice daily on days 1–14) and intravenous oxaliplatin (130 mg/m² on day 1), every 3 weeks. The primary end-point was the objective response rate, and secondary end-points included progression-free survival (PFS), overall survival (OS) and toxicity profiles.

Results: Fifty-five HER2-positive AGC patients were enrolled between August 2011 and February 2013. The median age was 57 years (range = 29–74). The confirmed objective response rate

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was 67% (95% confidence interval (CI) = 54–80%). After a median follow-up period of 13.8 months (range = 6.1–23.9), the median PFS and OS were 9.8 months (95% CI = 7.0–12.6) and 21.0 months (95% CI = 6.4–35.7), respectively. Frequently encountered grade 3–4 toxicities included neutropenia (18%), anaemia (11%), and peripheral neuropathy (11%). There was a treatment-related death caused by severe diarrhoea and complicated sepsis.

Conclusion: Combination of trastuzumab and XELOX is well tolerated and highly effective in patients with HER2-positive AGC.

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1. Introduction

Gastric cancer is a major worldwide cause of cancer-related deaths [1,2]. With recent advancements in our understanding of gastric cancer biology, human epidermal growth factor receptor 2 (HER2) has been recognised as a major target for novel therapies against metastatic or unresectable gastric cancer [3]. Because HER2 is overexpressed or amplified in 6–36% of gastric cancer cases [3–5], trastuzumab, a monoclonal antibody against HER2, was evaluated in a randomised phase III trial (Trastuzumab for Gastric Cancer: ToGA) for chemotherapy-naïve patients with HER2-overexpressing gastric cancer [6]. Adding trastuzumab significantly improves the efficacy of chemotherapy with 2.7 months of benefit in median overall survival (OS). Trastuzumab is the first biological agent approved for the treatment of gastric cancer, and its combination with cytotoxic chemotherapy is now considered a standard regimen for HER2-positive gastric cancer.

Although there is no single standard cytotoxic chemotherapy regimen for metastatic or unresectable gastric cancer, doublet or triplet regimens including fluoropyrimidine and platinum are considered standard therapies for metastatic or unresectable gastric cancer [7]. Previous randomised phase III trials demonstrate the non-inferiority of capecitabine and oxaliplatin to infusional fluorouracil and cisplatin, respectively, in terms of efficacy [8–10]. It is now widely accepted that capecitabine and oxaliplatin can be used as substitutes for infusing fluorouracil and cisplatin, respectively, and comparable efficacy and different safety profiles are expected.

In the pivotal ToGA trial [6], capecitabine plus cisplatin (XP) or fluorouracil plus cisplatin (FP) were used as the backbone chemotherapies in combination with trastuzumab. Most patients in this trial received XP (88%). Among the various standard regimens for gastric cancer, however, it remains uncertain which backbone regimen is optimal for combination with trastuzumab in terms of efficacy and safety. The combination of capecitabine and oxaliplatin (XELOX) is the preferred standard first-line regimen for metastatic or unresectable gastric cancer. In previous trials on gastric cancer that included exploratory analyses, oxaliplatin-containing regimens demonstrated favourable toxicity profiles and

potentially better outcomes in comparison to cisplatin-containing regimens [9–11]. However, the combination of trastuzumab and XELOX has not been investigated previously. Therefore, we conducted our present multicenter phase II trial to assess the efficacy and safety of trastuzumab plus XELOX.

2. Materials and methods

This multicenter, open-label, single arm, phase II trial was conducted at seven tertiary referral hospitals in Korea. The protocol was approved by the institutional review board of each participating institution, and all patients provided written informed consent prior to study entry. This study was conducted in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice (ClinicalTrials.gov Identifier: NCT01396707).

2.1. Eligibility

Histologically confirmed HER2-positive adenocarcinomas of the stomach or esophagogastric junction were considered eligible for this trial if the patient was chemotherapy-naïve and had inoperable locally advanced or metastatic disease. HER2 positivity was defined as either immunohistochemistry (IHC) 2+/fluorescence *in-situ* hybridisation (FISH)+ or IHC3+ according to the gastric cancer scoring system for HER2 [4,12]. For initial enrolment, HER2 positivity was determined by the local pathologists at each participating institution. However, all tumours were subsequently tested and centrally reviewed for HER2 status during the first cycle by an experienced pathologist (Y.S.P.). Patients were replaced if HER2 status was negative on this review. Inclusion criteria also included age ≥ 20 years; ≥ 1 measurable lesion according to Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 criteria [13]; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; adequate bone marrow, renal, and hepatic function; adequate cardiac function (left ventricular ejection fraction $\geq 50\%$ according to echocardiography or multigated acquisition [MUGA] scan); life expectancy ≥ 3 months; and written informed consent provided. Patients were excluded if they had received chemotherapy for gastric cancer. However, previous

adjuvant chemotherapy without platinum was allowed if the interval between the completion of adjuvant chemotherapy and study entry was >6 months. Patients were also excluded if they had a serious medical condition that was clinically significant and required active intervention.

2.2. Treatment

Patients received intravenous trastuzumab (8 mg/m² for the first cycle and 6 mg/m² for the subsequent cycles on day 1) plus oral capecitabine (twice-daily 1000 mg/m² on days 1–14) and intravenous oxaliplatin every 3 weeks (130 mg/m² on day 1). Treatment continued until disease progression, intolerable toxicity or patient's withdrawal of consent. Doses were interrupted or modified for grade 3–4 haematological toxicities (except anaemia) and grade 2–4 non-haematological toxicities according to the protocol. If XELOX was interrupted for >3 weeks due to any toxicity, chemotherapy was permanently discontinued but trastuzumab was allowed to continue at the discretion of attending physician if the toxicities were mainly caused by chemotherapy.

2.3. Assessment

Baseline assessments included medical history, physical examination, laboratory tests, MUGA scanning, chest X-ray and CT scanning of the abdomen and pelvis. Physical examination and laboratory tests were performed at each treatment cycle. To evaluate treatment responses, CT scans were performed every two cycles or whenever there were signs or symptoms that indicated disease progression. Tumour responses were initially determined by the local investigators according to RECIST v1.1 criteria, and treatment decisions were made accordingly. Responses were centrally reviewed at the end of the study (M.-H.R, B.-Y.R and S.R.P). Complete (CR) and partial responses (PR) were confirmed >4 weeks after the initial identification of response. Toxicities were assessed every cycle and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). MUGA scans were repeated every 12 weeks.

2.4. Statistical analysis

The primary end-point was the overall response rate according to the local investigator assessment. Secondary end-points included progression-free survival (PFS), overall survival (OS) and safety. The Simon minimax two-stage design was used to estimate the sample size [14]. The estimated response rate of patients who receive XELOX is 40% according to available historical data (P0), and 15% improvement was expected by adding trastuzumab (two-sided overall alpha = 0.1;

power = 80%). After expecting a 10% drop-out rate, the target enrolment was 55 patients. In the first stage, 30 patients were considered and ≥11 objective responses (CR or PR) were required to proceed to the second stage of patient enrolment. At least 24 objective responses were needed to declare trastuzumab in combination with XELOX as effective. PFS was defined as the time from the initiation of study treatment to disease progression or death, whichever occurred first. OS was defined from the initiation of study treatment to death from any cause. The Kaplan–Meier method was used to estimate the time-to-event variables. Baseline and follow-up left ventricular ejection fractions were compared using the paired *t* test. All efficacy parameters were analysed based on the full analysis set, which included those patients who met the eligibility criteria. A two-sided *p* value <0.05 was considered statistically significant, and SPSS 18.0 (SPSS Inc., Chicago, IL) was used to perform the statistical analyses.

3. Results

3.1. Patients

Between 6th August 2011 and 23th February 2013, a total of 64 patients were screened for possible enrolment. Among these cases, eight patients who did not meet the eligibility criteria were excluded prior to the study treatment, and one patient was replaced due to the lack of HER2 positivity on central pathology review. Hence, 55 patients were eligible for this analysis. The baseline characteristics of the patients are summarised in Table 1. The median age was 57 years (range = 29–74 years), and two-thirds of the patients were male. Most patients initially presented with metastatic disease (82%). The lymph node was the most frequent metastatic site (76%), followed by the liver (49%) and peritoneum (27%). According to a central pathology review, IHC 3+ was identified in 89% of patients (*n* = 49) and IHC 2+/FISH+ in 11% (*n* = 6). Data cut-off for the final analysis was done on 2nd September 2013. At the time of analysis, study treatment was continuing in 16 patients without progression and had been discontinued in 39 patients; 31 patients due to disease progression or death, 4 patient's refusal, two patients due to no residual disease following surgical resection, and each for follow-up loss and adverse events.

3.2. Efficacy

The confirmed objective response rate was 68% (95% confidence interval [CI] = 54–80%) according to RECIST v1.1 (Table 2). CR and PR were achieved in 2 (4%) and 35 patients (64%), respectively. The disease control rate, defined as the proportion of patients demonstrating CR, PR, or stable disease, was 89% (95%

Table 1
Baseline characteristics.

Characteristics	No. (%)
Median age (range), y	57 (29–74)
Sex (male)	37 (66%)
ECOG performance status 0–1	51 (93%)
Disease status	
Recurrent after curative resection	8 (14%)
Initially metastatic	45 (82%)
Inoperable locally advanced	2 (4%)
HER2 status	
IHC 2+/ <i>FISH</i> +	6 (11%)
IHC 3+	49 (89%)
Metastasis site	
Any	53 (96%)
Liver	27 (49%)
Peritoneum	15 (27%)
Lung	11 (20%)
Bone	7 (13%)
Lymph node	42 (76%)

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

Table 2
Objective responses according to RECIST v1.1.

Response	No.
Complete response	2 (4%)
Partial response	35 (64%)
Stable disease	12 (21%)
Progressive disease	3 (5%)
Not evaluable*	3 (5%)
Confirmed objective response rate	68% (95% confidence interval (CI) = 54–80%)
Disease control rate	89% (95% CI = 78–95%)

* Could not be evaluated due to patient refusal to receive additional chemotherapy after the first cycle ($n = 2$) or early death prior to the first response evaluation ($n = 1$).

CI = 78–95%). In two patients who demonstrated remarkable responses (each in terms of CR and PR) and a complete disappearance of distant metastases, surgical resection of the primary tumour was performed. In these cases, no residual disease was found in surgical tissues. The tumour response could not be assessed in three patients because of a refusal to receive further chemotherapy after cycle 1 (2 patients) or early death prior to the first assessment (1 patient). After a median follow-up period of 13.8 months (range = 6.1–23.9 months), the median PFS was 9.8 months (95% CI = 7.0–12.6 months) and the 6-month PFS rate was 69% (Fig. 1). The median OS was 21.0 months (95% CI = 6.4–35.7 months), and the 1-year OS rate was 63%. The efficacy outcomes according to the central review were consistent with those made by the local investigators (overall response rate of 69%, median PFS of 8.6 months [95% CI = 7.4–9.9 months]). Follow-

ing progression to study treatment, 22 of 29 patients with disease progression received second-line chemotherapy, six patients received anti-HER2 therapy, one patient received mTOR inhibitor, and 15 received conventional chemotherapy.

3.3. Safety

A median of 10 cycles of capecitabine (range = 1–30), eight cycles of oxaliplatin (range = 1–30), and 10 cycles of trastuzumab (range = 1–30) were administered. The mean relative dose intensity (RDI; i.e. the total delivered dose as a percentage of the targeted dose per unit time) was maintained at 74% for capecitabine, 78% for oxaliplatin and 90% for trastuzumab during the seventh cycle of treatment (Fig. 2). Adverse events developed in $\geq 10\%$ of patients are listed in Table 3. There was one treatment-related death due to severe diarrhoea and complicated sepsis. The most common grade 3–4 adverse events were neutropenia (18%), followed by anaemia (11%), peripheral neuropathy (11%) and fatigue (5%). No patients developed heart failure following treatment. According to repeated MUGA scans, the left ventricular ejection fractions (mean \pm standard deviation) were $67.7 \pm 5.2\%$ (range = 55–79%), $67.1 \pm 4.8\%$ (range = 57–78%), $65.9 \pm 4.4\%$ (range = 58–76%), $66.2 \pm 4.5\%$ (range = 60–78%) and $66.6 \pm 5.0\%$ (range = 60–83%) at baseline, 3, 6, 9 and 12 months, respectively. There were no statistical differences in the left ventricular ejection fractions over time. No patients demonstrated $\geq 10\%$ decrease in left ventricular ejection fraction in comparison with baseline.

4. Discussion

Our current study suggests that the combination of trastuzumab and XELOX is well tolerated and highly efficacious in patients with HER2-positive gastric cancer. The toxicity profile of trastuzumab plus XELOX is comparable to XELOX alone according to previous phase II trials on patients with advanced gastric cancer (AGC) [15,16]. In our study cohort, trastuzumab plus XELOX demonstrated promising efficacy outcomes compared to the results of the ToGA trial, where trastuzumab was combined with XP in most patients [6]. These findings suggest that XELOX is a reasonable option for combination with trastuzumab in patients with HER2-positive advanced gastric cancer.

In this study, trastuzumab plus XELOX was found to be highly efficacious, demonstrating an objective response rate of 68%, a median PFS of 9.8 months and a median OS of 21.0 months. Considering that the median PFS in previous phase II trials on XELOX was reported to be 5.6–5.8 months in previously untreated patients with gastric cancer [15,16], our current results confirm that trastuzumab can enhance the

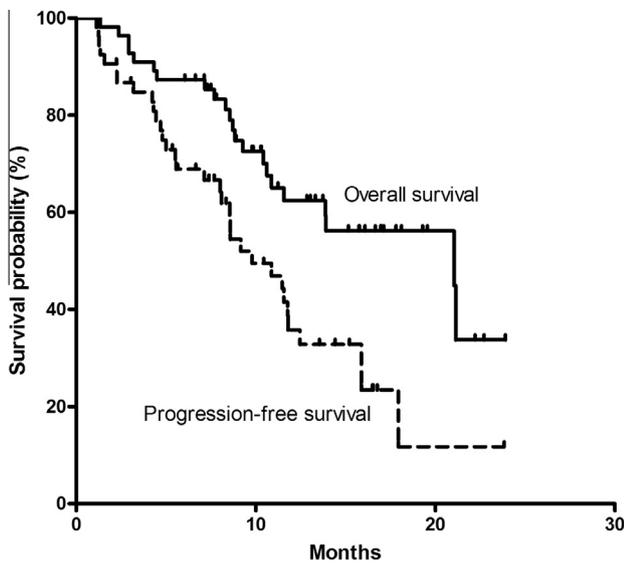


Fig. 1. Progression-free and overall survival.

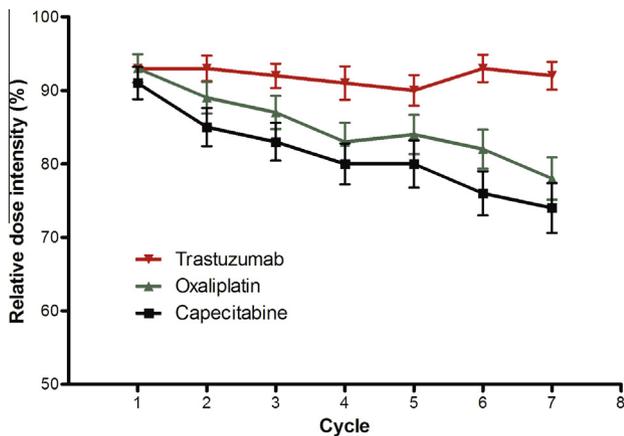


Fig. 2. Relative dose intensity.

efficacy of chemotherapy in HER2-positive gastric cancer. In the ToGA trial, the median PFS and OS of the trastuzumab plus XP/FP arm were 6.7 months and 13.8 months, respectively, and the response rate was 47% [6]. The outcomes of trastuzumab plus XELOX in our present study appeared to be superior to those of trastuzumab plus XP/FP reported in the ToGA trial, although direct comparisons between these trials should be cautiously interpreted (Table 4). One of the major reasons for the better outcomes identified in our present trial may be the higher proportion of patients with IHC 3+ HER2 gastric cancer in our cohort. The preplanned exploratory analysis of the ToGA trial showed that the impact of trastuzumab is correlated with the magnitude of HER2 positivity: median OS was 10.0 months and 16.0 months in patients with IHC 0 or 1+/FISH+, and IHC 2+/FISH+ or IHC 3+, respectively [6]. Whilst two-thirds of patients in the ToGA trial had tumours with high HER2 expression (51% for IHC 3+, and

Table 3
Adverse events occurring $\geq 10\%$ of patients.

	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	4 (7%)	17 (31%)	10 (18%)	–
Anaemia	24 (47%)	23 (42%)	5 (9%)	1 (2%)
Thrombocytopenia	28 (51%)	7 (13%)	1 (2%)	1 (2%)
Leukopenia	16 (29%)	11 (20%)	–	–
Anorexia	20 (36%)	9 (16%)	2 (4%)	–
Nausea	22 (40%)	7 (13%)	1 (2%)	–
Vomiting	9 (16%)	9 (16%)	–	–
Diarrhoea*	15 (27%)	5 (9%)	1 (2%)	–
Constipation	14 (25%)	3 (5%)	–	–
Stomatitis	10 (18%)	1 (2%)	1 (2%)	–
Abdominal pain	16 (29%)	5 (9%)	–	–
Fatigue	15 (27%)	12 (22%)	3 (5%)	–
Peripheral neuropathy	22 (40%)	11 (20%)	6 (11%)	–
Hand-foot syndrome	11 (20%)	6 (11%)	1 (2%)	–
Hyperpigmentation	22 (40%)	–	–	–
Weight loss	6 (11%)	2 (4%)	–	–

* One patient died of diarrhoea and complicated sepsis.

27% for IHC 2+/FISH+), all patients enrolled in our current study had high HER2-expressing tumours and most (89%) were diagnosed with HER2 IHC 3+ (for which better outcomes are anticipated with trastuzumab treatment). In the ToGA trial, ≤ 6 cycles of cytotoxic chemotherapy were allowed, whereas in our present trial, there were no limitations with regard to continuing the cytotoxic XELOX regimen if there was no disease progression or unacceptable toxicity. This might have affected the prolonged survival noted in our study cohort, considering that a median of 10 cycles of capecitabine and eight cycles of oxaliplatin were administered. It may therefore be a better strategy to continue administering backbone cytotoxic agents until disease progression or unacceptable toxicity, although there have been no clinical trials that have compared fixed chemotherapy cycles and continuing chemotherapy in advanced gastric cancer patients. Furthermore, a potential synergism between trastuzumab and oxaliplatin, which was suggested in a preclinical study, might have contributed to the promising results in this study [17].

Trastuzumab plus XELOX was generally well tolerated. The dose intensities of capecitabine, oxaliplatin and trastuzumab were well maintained during treatment. Here, the toxicity profile of trastuzumab plus XELOX was found to be comparable to XELOX, which was reported in previous phase II trials, although a higher incidence of grade 3–4 peripheral neuropathy (11% versus 0%), neutropenia (18% versus 10–14%) and anaemia (11% versus 0–2%) were noted with trastuzumab plus XELOX [15,16]. When our results were compared with the results of trastuzumab plus XP/FP obtained in the ToGA trial [6], trastuzumab plus XELOX demonstrated a favourable toxicity profile in terms of grade 3–4 neutropenia (18% versus 27%), anaemia (11% versus 18%) and gastrointestinal toxicities (nausea, 2% versus 7%; vomiting, 0% versus 6%; diarrhoea, 2%

Table 4
Cross-trial comparison of the current study with the ToGA trial.

	ToGA trial [6]	Current study
Definition of HER2-positive for study inclusion	IHC 3+ or FISH+ (IHC 2+/FISH+ or IHC 3+: 76%)	IHC 2+/FISH+ or IHC 3+
Backbone chemotherapy	Capecitabine plus cisplatin (88%) or fluorouracil plus cisplatin (12%), up to 6 cycles	Capecitabine plus oxaliplatin, no limitation on the number of cytotoxic chemotherapy cycles
Efficacy outcomes		
Response rate	47%	68%
PFS, median	6.7 months	9.8 months
OS, median	Overall: 13.8 months IHC 2+/FISH+ or IHC 3+ subgroup: 16.0 months	21.0 months

IHC, immunohistochemistry; FISH, fluorescence in-situ hybridisation; PFS, progression-free survival; OS, overall survival; HER2, human epidermal growth factor receptor 2.

versus 9%), except grade 3–4 peripheral neuropathy (11% versus 0%). Here, the frequency and severity of peripheral neuropathy were similar to the oxaliplatin-containing triplet regimens without trastuzumab documented by the REAL-2 trials (all grades, 80–84%; grades 3–4, 4–8%) [9]. In previous randomised trials that assessed substituting oxaliplatin for cisplatin for the treatment of gastric cancer, oxaliplatin-containing regimens demonstrated favourable safety profiles in comparison to cisplatin-containing regimens [9,10]. Furthermore, cisplatin has been found to be associated with increased thromboembolic events in comparison to oxaliplatin, and infusional fluorouracil was shown to be accompanied by the significant risk of central venous access device-related complications which required 10% of patients to have their device removed [9,18]. Taken together, our results suggest that XELOX is advantageous in terms of safety when combined with trastuzumab for the treatment of gastric cancer.

In conclusion, our study demonstrates that a combination of trastuzumab and XELOX has a favourable toxicity profile and promising efficacy in patients with metastatic or unresectable HER2-positive gastric cancer. Although our present study was not a randomised trial, our results provide background for further validation of XELOX as first-line backbone chemotherapy in combination with trastuzumab.

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Conflict of interest statement

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