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ORIGINAL ARTICLE

Safety and efficacy of trastuzumab administered as a 30-min infusion in patients with HER2-positive advanced gastric cancer

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Abstract

Purpose To investigate the safety and efficacy of 30-min maintenance infusions of trastuzumab in advanced gastric cancer positive for human epidermal growth factor receptor 2 (HER2).

Methods This was a retrospective study conducted across five Korean hospitals in patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma treated with first-line, 3-weekly trastuzumab plus chemotherapy. The first dose of trastuzumab (8 mg/kg) was administered as a 90-min infusion, with all subsequent maintenance infusions (6 mg/kg) given over 30 min. The primary aim was to investigate infusion-related reactions and cardiac events with 30-min infusions of trastuzumab. Objective response rate, progression-free survival, and overall survival were secondary endpoints.

Results The study included 128 patients (efficacy population), of whom 123 received both induction and maintenance infusions and formed the safety population. The median age was 63 years; 80% were presenting for the first time with metastatic disease, and 94% were treated with trastuzumab plus capecitabine/cisplatin. Infusion-related reactions were observed in 32 of 123 patients (26%). There were no cardiac events. The most frequent adverse events were anorexia and nausea, followed by vomiting, fatigue, mucositis, sensory neuropathy, and hand–foot syndrome. Most events were grade 1–2 and were manageable. No patient discontinued study treatment due to adverse events. The objective response rate was 63%, and included 6 complete responses.

Conclusions Trastuzumab 30-min maintenance infusions were well tolerated with a good safety profile, and resulted in sustained efficacy in patients with HER2-positive advanced gastric cancer.

Keywords 30-min infusion · Trastuzumab · Gastric cancer · Chemotherapy · Rapid infusion · HER2

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Introduction

Gastric cancer is the fifth most common malignancy and the third most common cause of cancer death worldwide [1]. Most patients present with inoperable advanced or metastatic disease [2–4]. This is because early gastric cancer generally has no symptoms, and physical signs are typically only seen in late disease [3]. The outlook for patients with gastric cancer is usually poor, with fewer than 30% of patients surviving for longer than 5 years [5]. Patients with advanced disease have a particularly poor prognosis, with 5-year survival less than 10% [4, 6].

Three countries in South-East Asia—China, Japan and Korea—account for 60% of all cases of gastric cancer worldwide [7]. The highest mortality rates are also seen in East Asia [1, 7]. In Korea, gastric cancer was, with the exception of thyroid cancer, the most common malignancy in 2014 [8]. Furthermore, it was the most common cancer in men, with a crude incidence of 79.2 per 100,000, and the fourth most common in women, with a crude incidence of 38.5 per 100,000. Overall, mortality due to gastric cancer was 17.6 per 100,000, making this type of malignancy the third leading cause of cancer death in Korea, after lung and liver tumors [8].

Research over the past decade has increasingly shown the importance of amplification of the human epidermal growth factor receptor 2 (*HER2/neu*) gene in gastric cancer. *HER2/neu* is an oncogene that is an important biomarker and driver of tumorigenesis in this disease. The HER2 protein is a transmembrane tyrosine kinase receptor and member of the epidermal growth factor receptor family [9]. Overexpression of the HER2 protein has been reported in up to 40% of patients with advanced gastric cancer [9–11] and is associated with poor outcomes and aggressive disease [9].

Trastuzumab is a humanized, recombinant monoclonal antibody that targets the HER2 protein by directly binding to the extracellular domain of the receptor, thereby preventing its cleavage. This inhibits HER2-mediated signaling and related tumor proliferation [9, 10]. Trastuzumab has well-established efficacy in breast cancer; durable tumor responses and improved outcomes have been reported in patients with early or metastatic HER2-positive disease [12–16].

More recently, trastuzumab has also demonstrated an emerging role in gastric cancer. Overall survival improvements were reported in HER2-positive advanced gastric cancer when trastuzumab was used in combination with chemotherapy in a landmark Phase III randomized trial in 594 patients across 122 centers in 24 countries [2]. As a result, trastuzumab given in combination with a platinum agent and 5-fluorouracil or capecitabine is now widely considered the standard of care for first-line therapy of patients with HER2-positive gastroesophageal junction or gastric cancer [4].

In patients with metastatic gastric cancer, trastuzumab is administered by intravenous infusion, typically over a period of 90 min for the loading dose, and 30–90 min for subsequent maintenance infusions. The manufacturer recommends dilution of the required dose in 250 mL normal saline [17]. Adverse events associated with trastuzumab administration include cardiac dysfunction and infusion-related reactions. Practitioners are required to monitor patients carefully during trastuzumab administration [17, 18] as the frequency and severity of infusion-related reactions with biologic agents is thought to be related to rates of infusion [19].

Reactions to trastuzumab infusions are much less common with maintenance infusions than with the first dose, particularly when premedication is used [20, 21]. This observation, together with consideration of patient convenience and comfort, and optimization of the use of clinic time, has led to interest in 30min trastuzumab infusions for maintenance therapy. Infusion of trastuzumab over this time period exhibits acceptable safety and tolerability in patients with breast cancer [19, 22, 23] (including in a study of 100 mL infusions [19]).

The present study was conducted to assess the adverse event profile of trastuzumab administered by 30-min intravenous infusion for maintenance therapy in patients with HER2-positive advanced gastric cancer. Secondary objectives were to explore response rates, progression-free survival, and overall survival.

Materials and methods

Study design and participants

This was a retrospective study conducted across five hospitals in Korea. Patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma treated with first-line trastuzumab plus chemotherapy (5-fluorouracil or capecitabine plus platinum) were selected for inclusion.

For inclusion in the study, patients were required to have: histologically confirmed gastric/gastroesophageal junction adenocarcinoma with a HER2 immunohistochemistry score of 3+ or HER2 immunohistochemistry 2+ and silver/fluorescence in situ hybridization (SISH/FISH [24, 25])-positive amplification; relapsed or metastatic disease; and first-line treatment with trastuzumab in combination with chemotherapy (capecitabine/cisplatin or 5-fluorouracil/cisplatin or capecitabine).

Patients were excluded if they had: histologically confirmed gastric/gastroesophageal junction non-adenocarcinoma (e.g., sarcoma, lymphoma, or squamous cell

carcinoma); HER2 immunohistochemistry 0/1+ or HER2 SISH/FISH-negative amplification; operable gastric cancer; or trastuzumab given as second-line or subsequent therapy.

The first dose of trastuzumab (8 mg/kg) was administered as a 90-min infusion in conjunction with chemotherapy. Chemotherapy consisted primarily of cisplatin 60–100 mg/m^2 intravenously on day 1 plus either capecitabine 1000 mg/m^2 orally twice a day from day 1 to day 14 or 5-fluorouracil 1000 mg/m^2 intravenously from day 1 to day 5 of each cycle. If tolerated, all subsequent maintenance doses of trastuzumab 6 mg/kg were administered over 30 min. All trastuzumab infusions were given in 250 mL of normal saline on day 1 of each cycle. Premedication, where used, consisted of chlorpheniramine 4 mg and/or hydrocortisone 100 mg or dexamethasone 5 mg, all by intravenous infusion over 10–15 min. Patients were to have received treatment every 3 weeks for up to 8 cycles.

The primary endpoint of the study was evaluation of adverse events, with particular focus on infusion-related reactions and cardiac events associated with 30-min infusion of trastuzumab. Adverse events were collected retrospectively from patient medical records and recorded using a standardized case report form (CRF). Infusion-related reactions were characterized by the following symptoms that occurred within 24 h of 30-min trastuzumab infusion: chills, nausea, vomiting, pain, headache, dizziness, dyspnea, hypotension, rash, asthenia, bronchospasm, anaphylaxis, angioedema, and hypoxia. Due to the retrospective nature of the study, there was no fixed method or timing for cardiac toxicity assessment. However, cardiac events were monitored at every cycle including left ventricular dysfunction, arrhythmias, hypertension, cardiac failure, and cardiomyopathy. The CRF also collected information on rare events associated with 30-min trastuzumab infusion, including skeletal abnormalities, neonatal death, interstitial pneumonitis, hypoxia, acute respiratory distress syndrome, pulmonary fibrosis, neutropenia, diarrhea, and sepsis. Events were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. The management of adverse events at participating centers was per standard practice and dependent on severity: grade 1 = no intervention; grade 2 = medication used as required; grade 3 or 4 = chemotherapy was stopped until recovery to grade 1 severity, then chemotherapy was continued at reduced dosages as necessary while trastuzumab was continued as usual.

Secondary endpoints were efficacy-related, and included objective response rate, progression-free survival and overall survival. Objective response rate was based on Response Evaluation Criteria in Solid Tumors (RECIST) [26] and was the total of complete and partial responses, assessed by the treating physician every 2 months. Progression-free survival was defined as the time from the first dose of chemotherapy to relapse or last follow-up or death; overall survival was the time from the first dose of chemotherapy to last follow-up or death.

The safety population consisted of all patients who received induction and at least one maintenance dose of trastuzumab. The efficacy population was defined as all patients who received the loading dose and maintenance infusions, or the loading dose only.

Assessments and data handling

Tumors were tested by a central laboratory for HER2 status with immunohistochemistry (HercepTest, Dako, Denmark) and FISH (HER2 FISH pharmDx, Dako) or SISH [24, 25]. Because of the inherent biological differences between breast and gastric tumors, notably tumor heterogeneity and the occurrence of basolateral membrane staining, a new set of immunohistochemistry scoring criteria were developed that are specific for gastric cancer. These scoring criteria were modified on the basis of the study by Hofmann and colleagues [10]. Patients were eligible if their tumor samples were scored as 3+ on immunohistochemistry or if they were FISH or SISH-positive (HER2: chromosome enumeration probe 17 [CEP17] ratio ≥ 2) [2].

Time-to-event data were estimated using the Kaplan–Meier method. The Cox proportional hazards model was used to estimate 95% confidence intervals for risk assessments. All analyses were conducted using statistical package for social sciences (SPSS) Version 20.0 for Windows.

Ethical statement

The study was approved by institutional review boards at all participating centers (DAUH-IRB-17-198) and performed according to the principles of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

Results

Patient characteristics and treatment exposure

In total, 128 patients with advanced gastric cancer were enrolled in the study between July 2011 and September 2017. This group included five patients who received induction therapy only, and was designated as the efficacy population. The safety population excluded these five individuals and consisted of 123 patients.

Baseline demographic and clinical characteristics are summarized in Table 1. The 128 patients in the efficacy population had a median age of 63 years (range

Table 1 Baseline demographic and clinical characteristics (efficacy population)

Characteristic	
Total number of patients	128
Sex, *n* (%)	
Male	103 (80.5)
Female	25 (19.5)
Age, years	
Median at diagnosis (range)	63 (20–87)
≤ 60 years, *n* (%)	44 (34.4)
> 60 years, *n* (%)	84 (65.6)
ECOG PS, *n* (%)	
0–1	123 (96.1)
2	5 (3.9)
Initial presentation, *n* (%)	
Relapse	26 (20.3)
Initial metastasis	102 (79.7)
History of surgery, *n* (%)	
No	93 (72.7)
Yes	35 (27.3)
Palliative	26 (20.3)
Curative	9 (7.0)
Number of metastases, *n* (%)	
1	77 (60.2)
2	33 (25.8)
≥ 3	18 (14.0)
Site of metastases, *n* (%)	
Liver	51 (39.8)
Peritoneal seeding	31 (24.2)
Distant lymph node(s)	59 (46.1)
HER2 status, *n* (%)	
IHC 3+	117 (91.4)
IHC 2+ and FISH+	11 (8.6)
Chemotherapy regimen, *n* (%)	
Capecitabine + cisplatin	120 (93.8)
5-FU + cisplatin	4 (3.1)
Capecitabine + oxaliplatin	3 (2.8)
5-FU	1 (0.8)

ECOG PS Eastern Cooperative Oncology Group performance status, *FISH* fluorescence *in situ* hybridization, *5-FU* 5-fluorouracil, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry

20–87 years); two-thirds were aged over 60 years, and 80.5% were men. Most patients (79.7%) were presenting for the first time with metastatic disease. Most (nearly three-quarters) had not had prior surgery, and the majority (60.2%) had one metastatic site. Most patients had good performance status (0–1: 96.1%), and most (93.8%) were treated with trastuzumab in combination with capecitabine/cisplatin (three patients received oxaliplatin rather than cisplatin, four patients received 5-fluorouracil in combination with cisplatin, and one further patient received 5-fluorouracil only).

Table 2 Adverse events (number of patients) with trastuzumab 30-min maintenance infusion ($N = 123$; safety population)

	Grade[a]			
	1	2	3	4
Hematologic adverse events, *n* (%)				
Anemia	3 (2.4)	1 (0.8)	–	–
Leukopenia	–	3 (2.4)	3 (2.4)	–
Thrombocytopenia	2 (1.6)	–	–	–
Other adverse events, *n* (%)				
Anorexia	12 (9.8)	6 (4.9)	1 (0.8)	1 (0.8)
Nausea	11 (8.9)	8 (6.5)	2 (1.6)	2 (1.6)
Vomiting	4 (3.3)	4 (3.3)	–	1 (0.8)
Fatigue	7 (5.7)	7 (5.7)	–	–
Mucositis	7 (5.7)	5 (4.1)	1 (0.8)	
Sensory neuropathy	8 (6.5)	4 (3.3)	1 (0.8)	
Hand–foot syndrome	7 (5.7)	6 (4.9)	–	–
Skin pigmentation	4 (3.3)	1 (0.8)	–	–
Constipation	2 (1.6)	–	–	–
Hiccups	–	1 (0.8)	–	–
Edema	2 (1.6)	–	–	–
Hoarseness	1 (0.8)	–	–	–

[a]National Cancer Institute Common Terminology Criteria for Adverse Events v4.03

The median number of trastuzumab plus chemotherapy treatment cycles was 6 (range 1–17) and the median number of trastuzumab single agent maintenance cycles was 3 (range 0–61). In total, 1458 cycles of treatment were given (839 cycles of trastuzumab plus chemotherapy and 619 cycles of trastuzumab single maintenance).

Most patients received premedication: 74 (57.8%) received corticosteroids with antihistamines, and 46 (35.9%) received antihistamines alone. Six patients (4.7%) received corticosteroids alone, and two patients (1.6%) received no premedication.

Safety

Overall, infusion-related reactions (nausea and vomiting) were observed in 32 of 123 patients (26.0%; Table 2); all infusion-related reactions were reported during trastuzumab plus chemotherapy combination treatment. No cardiac adverse events were observed. Most adverse events were mild to moderate (grade 1–2), and the most frequently reported were anorexia and nausea, followed by vomiting, fatigue, mucositis, sensory neuropathy, and hand–foot syndrome (Table 2). All events were considered treatment-related and were observed during therapy with trastuzumab plus chemotherapy.

Grade 1 or grade 2 anorexia was reported by 12 (9.8%) and six (4.9%) patients, and grade 1 or grade 2 nausea was reported by 11 (8.9%) and eight patients (6.5%), respectively (Table 2). Most hematologic adverse events were also grade 1–2. Three patients reported grade 3 leukopenia (Table 2). Other grade 3–4 events were observed in nine patients (predominantly anorexia and nausea). All events were manageable and none of the patients withdrew from study treatment because of adverse events.

Four patients switched from their original trastuzumab treatment to therapy with the trastuzumab biosimilar CT-P6 (CELLTRION, Inc. Incheon, Republic of Korea) during the maintenance period. No infusion-related reactions or cardiac events were reported after these changes of therapy.

Tumor response and survival

The objective response rate was 62.5%, and included six complete responses (Table 3). Median progression-free survival was 11.6 months (95% confidence intervals 7.5–15.7 months) (Fig. 1a) and median overall survival was 14.8 months (95% confidence intervals 11.9–17.7 months) (Fig. 1b).

Table 3 Tumor response rates ($N = 128$; efficacy population)

Best response	No. of patients (%)
Overall objective response	80 (62.5)
Complete response	6 (4.7)
Partial response	74 (57.8)
Stable disease	23 (18.0)
Progressive disease	16 (12.5)
Not evaluable	9 (7.0)

Discussion

In this retrospective study, over a total of 1458 cycles of treatment, 26% of the 123 patients included in the safety population experienced infusion-related reactions, most of which were mild to moderate in intensity. Grade 3–4 infusion-related reactions were infrequent, and adverse events were manageable. The large majority of the 128 enrolled patients tolerated 30-min infusions of trastuzumab, with maintenance of antitumor efficacy. These data suggest that rapid maintenance infusions of trastuzumab may, therefore, be feasible, and could potentially offer greater convenience than longer infusions, for patients with gastric cancer.

We note that frequencies of adverse events in the present cohort appear lower than in the ToGA study: for example, approximately 20% of patients reported nausea compared with up to two-thirds of patients in ToGA. Moreover, 16% and 7% of patients reported anorexia and vomiting in the present study, respectively, compared with approximately 50% each in ToGA [2]. No cases of asthenia, chills, dyspnea, and diarrhea were reported in the current study compared with 19%, 8%, 3%, and 37% of the ToGA population, respectively [2]. In addition, 68% of patients in the ToGA study reported Grade 3 or 4 adverse events [2], whereas most adverse events in our study were Grade 1 or 2 in severity. These differences are likely related to the much smaller number of patients in our study and the retrospective nature of the analysis. Additionally, although a regimen of cisplatin

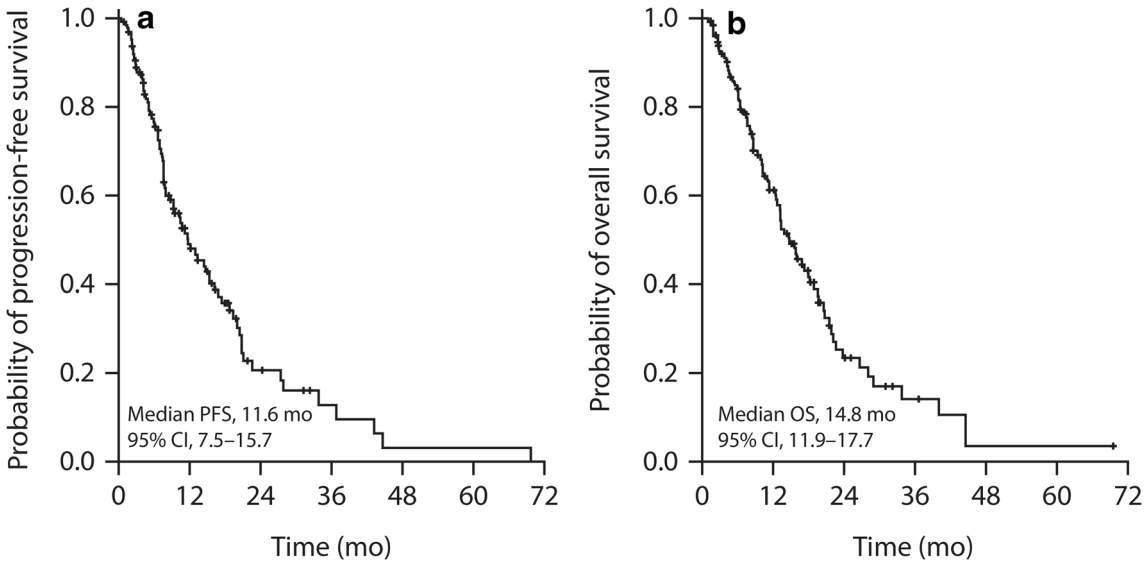

Fig. 1 Kaplan–Meier curves for **a** progression-free survival and **b** overall survival ($N = 128$; efficacy population). *CI* confidence interval, *Mo* months, *OS* overall survival, *PFS* progression-free survival

plus capecitabine or fluorouracil was used in both studies, the dosing regimen differed, particularly with respect to the cisplatin dose, which was 80 mg/m^2 in ToGA (although chemotherapy dose adjustments were allowed) and varied between 60 and 100 mg/m^2 in the current study. The percentage of patients who received different doses of cisplatin in the 60–100 mg/m^2 range was not recorded in our retrospective study, and this may have contributed, at least in part, to some of the differences observed in the safety profile between the present study and ToGA. Moreover, in the current study, premedication to prevent chemotherapy-induced nausea and vomiting was allowed but information on its usage was not recorded. Therefore, the influence of this premedication on the incidence of trastuzumab-associated infusion-related reactions remains undefined. These observations highlight the caution required when comparing and contrasting findings from studies involving different cohorts of patients. However, we note that the overall pattern of adverse events was similar in both studies.

The present 30-min infusion data may also be contrasted with those from patients with HER2-positive breast cancer (again acknowledging the limitations inherent in indirect comparisons with different disease types and chemotherapies). For example, Abe et al. reported very low frequencies of adverse events and no cardiac concerns associated with 30-min trastuzumab infusions in a study of 31 women [19]. In that study, trastuzumab was administered at a dose of 8 mg/kg as a 250 mL 90-min infusion followed by 6 mg/kg in 100 mL over 30 min in 3-week cycles. Grade 2 infusion reactions were noted in two patients following the initial dose; there were no infusion reactions thereafter [19]. It should be noted that only 23% of these patients had metastatic disease; 77% were receiving adjuvant therapy. Thus, this population had less advanced cancer than our cohort of gastric cancer patients.

Similar findings were reported by Ring et al. in an audit of 85 patients with breast cancer who received a total of 201 30-min infusions of trastuzumab over a 7-month period [23]. Of these patients, 34% received premedication with antihistamines and/or corticosteroids. A total of 54 women (64%) were receiving adjuvant treatment and 31 (36%) palliative therapy. Three infusion reactions were recorded over the observation period, two of which were of grade 1 severity. A grade 3 reaction (throat tightening) resolved after administration of further hydrocortisone and chlorpheniramine and was deemed possibly related to anxiety. The authors concluded that most patients can tolerate 30-min infusions of trastuzumab, with infusion reactions being rare and manageable in the outpatient setting [23].

The tumor response rates we observed are comparable to those previously reported in patients with advanced gastric cancer. The overall tumor response rate in ToGA was 47% (5% complete response rate) [2], compared with an objective response rate of 63% (5% complete response rate) in the present study. The median progression-free survival and median overall survival in ToGA were 6.7 months and 13.8 months, respectively, compared with 11.6 and 14.8 months in the present study. It is reasonable to expect that some benefit in progression-free survival will carry over into overall survival. The relatively short survival post-progression observed in our study may reflect the small sample size or other factors that were not recorded, and therefore, not considered in this retrospective study, such as variability in treatment decisions made after disease progression. Clinical studies investigating HER2-targeted agents in combination with salvage palliative chemotherapy are needed.

As reported earlier, four patients in this study transferred to the trastuzumab biosimilar CT-P6. These treatment switches were not associated with any safety or tolerability concerns during maintenance therapy.

The use of 30-min infusions of trastuzumab in patients with advanced gastric cancer has implications for patient convenience and for optimal use of chemotherapy unit capacity, as has been previously noted in patients with breast cancer [23]. Shorter infusion times have similar implications in other oncology settings, with authors reporting that longer infusion times cause increased physician, nurse and administrative staff time and workloads, and inconvenience to patients [27, 28].

Our study is subject to a number of limitations, most notably its retrospective, noncomparative design, with no control arm. As such, any comparisons and contrasts must, by necessity, be made indirectly with other studies with different patient populations and designs. Limitations of this study include those that are associated with retrospective patient record review studies of this nature, particularly the potential for information bias. As not all information may have been recorded reliably in the patient record, there is the possibility that the incidence of adverse events, including infusion-related reactions, may have been inaccurately estimated. Moreover, record review studies rely upon the data that are available, and some information of interest may not have been recorded. For instance, in the present study, there was no defined method for assessing cardiac adverse events, insufficient information available for analysis regarding the incidence of infusion-related reactions per dose, no information regarding the relationship between infusion-related reactions and the number of cycles, and the management of infusion-related reactions in clinical practice. Although there were no clear criteria for the discrimination of trastuzumab-related infusion-related reactions from cisplatin-related infusion reactions, typical trastuzumab-related infusion-related reactions (including hypersensitivity, chills, fever, skin redness/itching) were not reported in the present study. Furthermore, no infusion-related reactions were reported during trastuzumab single agent maintenance cycles, and

all infusion-related reactions (nausea and vomiting) were reported during trastuzumab plus chemotherapy combination treatment. As such, the infusion-related reactions (nausea and vomiting) reported in the present study could be related to 5-fluorouracil or cisplatin. Despite these limitations, we suggest that our findings represent a useful 'real-world' illustration of the safety of shorter infusion durations of maintenance trastuzumab in patients with advanced gastric cancer. Moreover, as the first data of its kind in patients with gastric cancer, the study represents a basis for future prospective investigation of shorter infusions of trastuzumab in this setting.

In conclusion, the present study provides an example of current clinical practice, showing that trastuzumab 30-min maintenance infusions were well tolerated, had an acceptable safety profile, and resulted in sustained efficacy in patients with HER2-positive advanced gastric cancer.

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Author contributions SYO and JGK were involved in study conception and design, acquisition of data, and analysis/interpretation of data. SJH, BWK, HJL, and JHK were involved in acquisition of data, and analysis/interpretation of data. JL, SL, STK, SHP, JHK, HYL, and WKK were involved in acquisition of data. HK was involved in analysis and interpretation of data. All authors had full access to all the data in the study, reviewed drafts of the manuscript, approved the final version, had final responsibility for the decision to submit for publication, and agree to be accountable for the work.

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Compliance with ethical standards

Conflict of interest HoUng Kim is an employee of CELLTRION Healthcare Co., Ltd. All other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

References

1. World Health Organization. International Agency for Research on Cancer (2012) GLOBOCAN 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 14 Mar 2018
2. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Ruschoff J, Kang YK (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376(9742):687–697. https://doi.org/10.1016/s0140-6736(10)61121-x
3. Cabebe EC (2018) Gastric cancer. Practice essentials. Medscape, LLC. https://emedicine.medscape.com/article/278744-overview. Accessed 15 Mar 2018
4. Orditura M, Galizia G, Sforza V, Gambardella V, Fabozzi A, Laterza MM, Andreozzi F, Ventriglia J, Savastano B, Mabilia A, Lieto E, Ciardiello F, De Vita F (2014) Treatment of gastric cancer. World J Gastroenterol 20(7):1635–1649. https://doi.org/10.3748/wjg.v20.i7.1635
5. den Hoed CM, Kuipers EJ (2016) Gastric cancer: how can we reduce the incidence of this disease? Curr Gastroenterol Rep 18(7):34. https://doi.org/10.1007/s11894-016-0506-0
6. Lee JS, Kim SH, Im SA, Kim MA, Han JK (2017) Human epidermal growth factor receptor 2 expression in unresectable gastric cancers: relationship with CT characteristics. Korean J Radiol 18(5):809–820. https://doi.org/10.3348/kjr.2017.18.5.809
7. Fock KM (2014) Review article: the epidemiology and prevention of gastric cancer. Aliment Pharmacol Ther 40(3):250–260. https://doi.org/10.1111/apt.12814
8. Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH, Community of Population-Based Regional Cancer Registries (2017) Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2014. Cancer Res Treat 49(2):292–305. https://doi.org/10.4143/crt.2017.118
9. Gravalos C, Jimeno A (2008) HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol 19(9):1523–1529. https://doi.org/10.1093/annonc/mdn169
10. Hofmann M, Stoss O, Shi D, Buttner R, van de Vijver M, Kim W, Ochiai A, Ruschoff J, Henkel T (2008) Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology 52(7):797–805. https://doi.org/10.1111/j.1365-2559.2008.03028.x
11. Liu X, Xu P, Qiu H, Liu J, Chen S, Xu D, Li W, Zhan Y, Li Y, Chen Y, Zhou Z, Sun X (2016) Clinical utility of HER2 assessed by immunohistochemistry in patients undergoing curative resection for gastric cancer. Onco Targets Ther 9:949–958. https://doi.org/10.2147/OTT.S100979
12. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, Scholl S, Fehrenbacher L, Wolter JM, Paton V, Shak S, Lieberman G, Slamon DJ (1999) Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 17(9):2639–2648. https://doi.org/10.1200/jco.1999.17.9.2639
13. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Lang I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Ruschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353(16):1659–1672. https://doi.org/10.1056/NEJMoa052306
14. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive

breast cancer. N Engl J Med 353(16):1673–1684. https://doi.org/10.1056/NEJMoa052122
15. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, Slamon DJ, Murphy M, Novotny WF, Burchmore M, Shak S, Stewart SJ, Press M (2002) Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 20(3):719–726. https://doi.org/10.1200/jco.2002.20.3.719
16. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783–792. https://doi.org/10.1056/nejm200103153441101
17. Genentech Inc (2017) Highlights of prescribing information. Herceptin® (trastuzumab) for injection, for intravenous use. https://www.gene.com/download/pdf/herceptin_prescribing.pdf. Accessed 12 June 2018
18. Lenz HJ (2007) Management and preparedness for infusion and hypersensitivity reactions. Oncologist 12(5):601–609. https://doi.org/10.1634/theoncologist.12-5-601
19. Abe H, Mori T, Kawai Y, Tomida K, Yamazaki K, Kubota Y, Umeda T, Tani T (2013) Safety assessment of intravenous administration of trastuzumab in 100 ml saline for the treatment of HER2-positive breast cancer patients. Asian Pac J Cancer Prev 14(8):4843–4846
20. Baselga J, Carbonell X, Castaneda-Soto NJ, Clemens M, Green M, Harvey V, Morales S, Barton C, Ghahramani P (2005) Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. J Clin Oncol 23(10):2162–2171. https://doi.org/10.1200/jco.2005.01.014
21. Cook-Bruns N (2001) Retrospective analysis of the safety of Herceptin immunotherapy in metastatic breast cancer. Oncology 61(Suppl 2):58–66. https://doi.org/10.1159/000055403
22. Abe H, Umeda T, Kawai Y, Tanaka M, Mori T, Cho H, Kubota Y, Mekata E, Kurumi Y, Tani T (2010) Adjuvant trastuzumab can be infused safely over 30 minutes. Gan To Kagaku Ryoho 37(10):1887–1891
23. Ring A, Simcock R, Mitra S, Bloomfield D, King J, Simpson S, Sadler G, Webb A (2008) Infusion of trastuzumab maintenance doses over 30 minutes. Ann Oncol 19(8):1509–1510. https://doi.org/10.1093/annonc/mdn390
24. Papouchado BG, Myles J, Lloyd RV, Stoler M, Oliveira AM, Downs-Kelly E, Morey A, Bilous M, Nagle R, Prescott N, Wang L, Dragovich L, McElhinny A, Garcia CF, Ranger-Moore J, Free H, Powell W, Loftus M, Pettay J, Gaire F, Roberts C, Dietel M, Roche P, Grogan T, Tubbs R (2010) Silver in situ hybridization (SISH) for determination of HER2 gene status in breast carcinoma: comparison with FISH and assessment of interobserver reproducibility. Am J Surg Pathol 34(6):767–776. https://doi.org/10.1097/PAS.0b013e3181d96231
25. Dietel M, Ellis IO, Hofler H, Kreipe H, Moch H, Dankof A, Kolble K, Kristiansen G (2007) Comparison of automated silver enhanced in situ hybridisation (SISH) and fluorescence ISH (FISH) for the validation of HER2 gene status in breast carcinoma according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists. Virchows Arch 451(1):19–25. https://doi.org/10.1007/s00428-007-0424-5
26. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45(2):228–247. https://doi.org/10.1016/j.ejca.2008.10.026
27. Tobinai K, Klein C, Oya N, Fingerle-Rowson G (2017) A review of obinutuzumab (GA101), a novel type II anti-CD20 monoclonal antibody, for the treatment of patients with B-Cell malignancies. Adv Ther 34(2):324–356. https://doi.org/10.1007/s12325-016-0451-1
28. Pritchard CH, Greenwald MW, Kremer JM, Gaylis NB, Rigby W, Zlotnick S, Chung C, Jaber B, Reiss W (2014) Safety of infusing rituximab at a more rapid rate in patients with rheumatoid arthritis: results from the RATE-RA study. BMC Musculoskelet Disord 15:177. https://doi.org/10.1186/1471-2474-15-177