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

Min-Hee Ryu [a,1], Changhoon Yoo [a,1], Jong Gwang Kim [c], Baek-Yeol Ryoo [a], Young Soo Park [b], Sook Ryun Park [a], Hye-Suk Han [d], Ik Joo Chung [e], Eun-Kee Song [f], Kyung Hee Lee [g], Seok Yun Kang [h], Yoon-Koo Kang [a,*]

[a] *Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[b] *Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[c] *Department of Oncology/Hematology, Kyungpook National University Medical Center, Daegu, South Korea*
[d] *Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea*
[e] *Department of Internal Medicine, Chonnam National University Medical School, Gwangju, South Korea*
[f] *Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, South Korea*
[g] *Department of Internal Medicine, Yeungnam University Medical Center, Yeungnam University College of Medicine, Daegu, South Korea*
[h] *Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, South Korea*

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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+/fluorescence *in-situ* hybridisation (FISH)+ received intravenous trastuzumab (8 mg/m^2 for first cycle and 6 mg/m^2 for subsequent cycles on day 1) plus oral capecitabine (1000 mg/m^2 twice daily on days 1–14) and intravenous oxaliplatin (130 mg/m^2 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

* *Corresponding author at:* Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 138-736, South Korea. Tel.: +82 2 3010 3230; fax: +82 2 3010 8772.
E-mail address: ykkang@amc.seoul.kr (Y.-K. Kang).
[1] M.-H. Ryu and C. Yoo contributed equally and should be considered co-first authors.

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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.

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 (ClinicalTrial.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-naive 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 $\geqslant$20 years; $\geqslant$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 $\geqslant$50% according to echocardiography or multigated acquisition [MUGA] scan); life expectancy $\geqslant$3 months; and written informed consent provided. Patients were excluded if they had received chemotherapy for gastric cancer. However, previous