Docetaxel, oxaliplatin, 5FU, and trastuzumab as first-line therapy in patients with human epidermal receptor 2-positive advanced gastric or gastroesophageal junction cancer

Preliminary results of a phase II study

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Abstract
The aim of this study is to report first preliminary results of patients enrolled in a phase II study that will investigate the activity and safety of docetaxel, oxaliplatin, and 5-fluorouracil (DOF) in combination with trastuzumab in human epidermal receptor-2 (HER-2) positive patients with advanced gastric or gastroesophageal junction (GEJ) cancer.

Treatment consisted of docetaxel 70 mg/m\textsuperscript{2} combined with oxaliplatin 130 mg/m\textsuperscript{2} on day 1, and continuous infusion 5-fluorouracil mg/m\textsuperscript{2} days 1–5 plus trastuzumab at the standard dose on day 1, every 3 weeks for a maximum of 8 cycles.

Fifteen patients were enrolled. The overall response rate was 60%. The median progression-free survival was 9.2 months (95% confidence interval [CI], 4.4–10.1 months) and the median overall survival was 19.4 months (95% CI, 8.9–21.1 months). Grade 3 neutropenia was observed in 3 patients (20%).

The DOF plus trastuzumab seems active in HER-2 positive advanced gastric or GEJ cancer, final results of the phase II study are awaited.

Abbreviations: CR = complete response, DCR = disease-control rate, DOF = docetaxel/oxaliplatin/5-FU, EOF = epirubicin/oxaliplatin/5-fluorouracil, GEJ = gastroesophageal junction, HER2 = human epidermal receptor 2, NCI = National Cancer Institute, OS = overall survival, PD = progressive disease, PFS = progression free survival, PR = partial response, SD = stable disease.

Keywords: docetaxel, fluorouracil, gastric cancer, human epidermal receptor-2, oxaliplatin, trastuzumab

1. Introduction
Gastric or gastroesophageal junction (GEJ) cancer is considered one of the most important cause of death related to cancer in Europe.\textsuperscript{[1]} Surgical resection is the standard for long-term curative results,\textsuperscript{[2,3]} unfortunately only one-third of patients are ideal candidates to radical surgery while for patients with locally advanced or metastatic disease at diagnosis, systemic chemotherapy with a platinum compound and a fluoropyrimidine is considered the standard of treatment.\textsuperscript{[4]} However, several studies have proposed a triplet drug combinations with the addition of taxane or antracycline\textsuperscript{[5]} and recently a metanalysis has suggested similar activity of docetaxel and epirubicin-based chemotherapeutic regimen.\textsuperscript{[6]} In this context, we previously reported that a sequential treatment with a triplet combination of epirubicin/oxaliplatin/5-fluorouracil (EOF) and docetaxel/oxaliplatin/5-FU (DOF) is active against metastatic gastroesophageal cancer.\textsuperscript{[6]}

Trastuzumab is a humanized recombinant monoclonal antibody that selectively binds to the extracellular domain of human epidermal receptor 2 (HER2).\textsuperscript{[7]} The trastuzumab for gastric cancer (ToGA) trial evaluated the combination of trastuzumab with a cisplatin/fluoropyrimidine chemotherapy doublet in patients with previously untreated advanced HER2-positive gastroesophageal cancer\textsuperscript{[8]} showing a survival benefit. However, little data are available on efficacy and toxicity of a triplet taxane-based regimen chemotherapy for HER2-positive gastroesophageal tumors. Therefore, we investigated the feasibility and preliminary efficacy of DOF chemotherapy in combination with trastuzumab as first line in patients with gastroesophageal cancer, hereby we report the results of first 15 patients with a brief overview of literature.
2. Methodology

The complete methodology is reported in supplementary data, http://links.lww.com/MD/C247, we briefly describe here for convenience. The study enrolled patients with histologically proven advanced adenocarcinoma of the stomach or GEJ HER2-positive tumors who had not previously received chemotherapy for advanced disease. The other eligibility criteria included age >18 years, Eastern Cooperative Oncology Group performance status of 0 to 1, bidimensionally measurable disease, a life expectancy of at least 6 months, adequate hematological and biochemical parameters, baseline left ventricular ejection fraction ≥50%. Patients with operable metastatic disease were excluded from the study, as were those with severe cardiac dysfunction, chronic diarrhea, or uncontrolled sites of infection. This study was approved by the local ethical and scientific committee, and all of the patients gave their written informed consent.

The pretreatment evaluation, performed within 2 weeks before study entry. During treatment, physical examination and blood test were mandatory before each course, and left ventricular ejection fraction was assessed every 3 month. Treatment response was evaluated every 4 3-weekly cycles or sooner if clinically indicated. Tumor response was assessed using the RECIST 1.1 criteria.19

Treatment consisted of intravenous (i.v.) docetaxel 70mg/m² combined with 6-hour i.v. 1-OHP 130mg/m² on day 1, and c.i. 5FU 750mg/m² days 1–5 (DOF regimen) plus trastuzumab intravenously as a 90-min infusion at doses of 8mg/kg (loading dose in first cycle) and 6mg/kg (maintenance doses) on day 1, every 3 weeks. This schedule was repeated until disease progression, development of unacceptable toxicity, or patient withdrawal of consent. After the completion of 8 cycles, the patients who achieved complete or partial response or stable disease continued the maintenance treatment with c.i. 5FU 750 mg/m² days 1–5 every 3 weeks and trastuzumab 6mg/kg until progressive disease or unacceptable toxicity.

Toxicity was assessed using the common toxicity criteria of the National Cancer Institute (NCI), version 3.0. Treatment was delayed if, on the planned day of treatment, the neutrophil count was <1,500/mm³, the platelet count was <100,000/mm³, or the patient had persistent diarrhea or stomatitis >grade 1. Any patient who required more than 2 weeks for recovery from adverse reactions was excluded from the study. In the event of grade 4 hematologic or any other severe (>grade 3) organ toxicity in individual patients, the doses of chemotherapy drugs were reduced by 25% for subsequent courses.

3. Statistical considerations

The primary end-point was 6-months disease-control rate (DCR). It was calculated that a total of 43 patients would have to be recruited. Progression free survival (PFS) was calculated as the time from the first chemotherapy infusion to disease progression or death. Secondary end points included: safety and overall survival (OS), measured from the date of start of treatment to the date of death. Kaplan–Meier method was used to determine PFS and OS. Statistical analyses were conducted by STATA IC 2012 software (StataCorp LLC, College Station, TX).

4. Results

From October 2011 to May 2017, a total of 15 patients were enrolled in the study. Baseline characteristics of the patients are presented in Table 1. The median age was 62 years (range, 45–74). All patients had a performance status of 0 or 1, and 66.7% had multiple metastatic sites. Primary tumor was gastric in 12 patients and GEJ in 3 patients. Two patients had received prior chemotherapy.

| Patient | Age | Sex | ECOG | Tumor location | Gastric cancer type | Primary tumor resected | No. of sites of disease | Previous adjuvant chemotherapy | HER2 status |
|---------|-----|-----|------|---------------|--------------------|-----------------------|------------------------|-------------------------------|------------|
| 1       | 62  | M   | 0    | Stomach       | Mixed              | Yes                   | 1                      | No                            | 3+         |
| 2       | 64  | M   | 0    | Stomach       | Intestinal         | No                    | 3                      | No                            | 3+         |
| 3       | 68  | M   | 1    | Gastroesophageal junction | Intestinal     | No                    | 2                      | No                            | 3+         |
| 4       | 74  | F   | 1    | Stomach       | Intestinal         | Yes                   | 2                      | Yes                           | 3+         |
| 5       | 45  | M   | 0    | Stomach       | Intestinal         | No                    | 1                      | No                            | 3+         |
| 6       | 60  | M   | 1    | Gastroesophageal junction | Intestinal     | No                    | 4                      | No                            | 3+         |
| 7       | 69  | F   | 0    | Stomach       | Diffuse            | No                    | 3                      | No                            | 3+         |
| 8       | 53  | F   | 0    | Stomach       | Intestinal         | Yes                   | 1                      | No                            | 3+         |
| 9       | 48  | M   | 0    | Stomach       | Mixed              | No                    | 6                      | No                            | 3+         |
| 10      | 63  | M   | 0    | Stomach       | Intestinal         | Yes                   | 2                      | No                            | 3+         |
| 11      | 65  | F   | 0    | Stomach       | Intestinal         | No                    | 2                      | No                            | 3+         |
| 12      | 38  | M   | 0    | Stomach       | Intestinal         | No                    | 1                      | No                            | 2+         |
| 13      | 71  | M   | 1    | Gastroesophageal junction | Diffuse        | Yes                   | 4                      | Yes                           | 3+         |
| 14      | 44  | F   | 1    | Stomach       | Mixed              | No                    | 3                      | No                            | 2+         |
| 15      | 54  | M   | 0    | Stomach       | Intestinal         | No                    | 1                      | No                            | 3+         |

HER2 = human epidermal receptor 2.
The median PFS of the patients was 9.2 months (95% CI, 4.4–10.1 months); 9 patients (60%) were progression-free after about 6 months from the onset of chemotherapy (Fig. 1). After the completion of 8 cycles of DOF, 8 patients started maintenance therapy. No patient was lost to follow-up. A total of 9 patients received a further treatment line at documentation of progressive disease (mainly ramucirumab-based therapy).

At a median follow-up time of 15.9 months, 11 patients were deceased: the median OS was 19.4 months (95% CI, 8.9–21.1 months) (Fig. 1).

Toxicity during DOF plus trastuzumab was acceptable and easily manageable with adequate supportive care (Table 1 supplementary data, http://links.lww.com/MD/C247). One patient interrupted DOF treatment after 3 cycles for toxicity-unrelated reasons. Three of 15 patients experienced at least 1 episode of grade 3 neutropenia without neutropenic fever.

Among non-hematologic toxicities, grade 4 was not observed: grade 3 nausea/vomiting, diarrhea, and stomatitis was reported in 2, 1, and 1 patient, respectively. A total of 11 DOF cycles were delayed for at least 1 week because of toxicity, and dose reductions were required in 3 patients.

No patient had an infusion reaction to trastuzumab and no moderate to severe cardiotoxicity was observed, a cardiac event consisting of a grade 1 atrial fibrillation was reported in 1 patient.

## 5. Discussion

The ToGA study demonstrated that trastuzumab in combination with cisplatin plus capecitabine or fluorouracil was superior to cisplatin plus capecitabine or fluorouracil alone[8] in term of tumor response, PFS and OS in patients with HER2-positive advanced gastric cancer. Based on this data, trastuzumab was approved in combination with chemotherapy as first line of treatment in patients with metastatic HER2-overexpressing gastric or GEJ adenocarcinoma. Although with the limitation of a small sample size, cisplatin and trastuzumab achieved a response rate in 32% of patients with a disease control in 64%. Median time to progression was 5.1 months, while data on OS were not reported. Another Japanese phase II study evaluated the efficacy and safety of S-1 plus cisplatin plus trastuzumab in HER2-positive advanced gastric cancer.[11] The authors enrolled a total of 54 patients and the response rate was 68%, and the disease control rate was 94%. Median OS, PFS, and time to treatment failure were 16.0, 7.8, and 5.7 months, respectively. Finally, TRIO-013/LOGiC was a multicenter, double-blind, randomized phase III study that evaluated the efficacy and safety of a fluorouracil alone[8] in term of efficacy of a first-line treatment with a DOF regimen plus trastuzumab with 9.2 months of median PFS and 19.4 months of median OS. These results compare well with the best ones reported in this disease for the HER2-positive gastric or GEJ cancer (Table 3). As known, these patients had a very poor outcome and survival. In addition, a preplanned exploratory analysis of the ToGA trial suggested that a strongest expression of HER2 (IHC 3+) is able to predict the survival of patients treated with trastuzumab with an improvement in OS of >5 months for patients with IHC 3+ compared with patients with IHC 2+ and subsequent FISH positive as definition of HER2-positivity. However, the nature of our results of the current study (preliminary data from a small sample size) is a limitation which should be considered for a correct their
In order to improve the efficacy of trastuzumab and chemotherapy in HER2 advanced metastatic gastric cancer, different approach or combinations have been tested. In 2016, Li et al.[22] reported the results of a phase II study which aims to analyze the benefit and risk associated with continuing trastuzumab treatments after first line progression, in addition, a multicenter, single-arm, phase II study had combined bevacizumab and trastuzumab with docetaxel, oxaliplatin, and capecitabine as first-line treatment of advanced HER2-positive gastric cancer.[23] However, although a certain efficacy has been observed, these approaches should be validated in larger randomized phase III studies. Finally, Pertuzumab, a new humanized anti-HER2 antibody, almost tested in breast cancer in combination with trastuzumab, has shown to achieve partial response in the 86% of HER2-positive advanced gastric cancer when combined with capecitabine and cisplatin chemotherapy.[24] Based on these results, the JACOB phase III study (a study of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastric cancer; NCT01774786) has been conducted and recently completed. The results of the JACOB study are awaited to define the role of pertuzumab in HER2-positive metastatic gastric cancer.

In summary, the conventional triple drug regimen DOF in combination with trastuzumab seems a feasible and encouraging option in HER2-positive advanced gastric or GEJ cancer. The final results of the phase II study are awaited to confirm these conclusions.

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**Table 3**

Main outcomes in patients with HER-2 positive gastric cancer treated with chemotherapy and trastuzumab.

| Study | Phase | Treatment | Number | Response rate (%) | PFS (mo) | OS (mo) | Reference |
|-------|-------|-----------|--------|-------------------|----------|---------|-----------|
| ToGA  | III   | CV/CF     | 131    | 35                | 6.7      | 17.9    | 8         |
| Grávalos et al | II     | C        | 22     | 32                | 5.1      | NR      | 10        |
| HERBIS-1 | II   | S+C      | 54     | 68                | 7.8      | 16.0    | 11        |
| Yi et al | Retrospective | CX or CF | 168    | 50.6              | 10.2     | 18.5    | 13        |
| Namikawa et al | Retrospective | CX | 15    | 46.7              | NR       | 22.9    | 14        |
| CSG01G001 | II | CAPOX    | 51     | 66.6              | 9.2      | 19.5    | 15        |
| Kataoka et al | II | CS-1     | 22     | 41.2              | 7.5      | 15.3    | 16        |
| Chua et al | II | CS-1     | 30     | 50.3              | 7.4      | 16.6    | 17        |
| Mitsui et al | II | DCS      | 16     | 93.8              | NR       | NR      | 18        |
| Soutar et al | Retrospective | mFOLFOX6 or XELOX | 34    | 41                | 9        | 17.3    | 19        |
| Ryu et al | II | XELOX    | 55     | 67                | 9.8      | 21      | 20        |
| Miura et al | II | SC       | 44     | 61                | 5.9      | 16.5    | 21        |
| Current study preliminary data | II | DOF+T | 15     | 60                | 9.2      | 19.4    | –         |

C = cisplatin, CAPOX = capecitabine + oxaliplatin, D = docetaxel, DOF = docetaxel + oxaliplatin + 5-FU, F = 5-FU, FISH = fluorescent in situ hybridization, HER2 = human epidermal receptor 2, mFOLFOX = modified oxaliplatin/5-FU/leucovorin, OS = overall survival, PFS = progression-free survival, S = S-1, T = trastuzumab, X = capecitabine, XELOX = oxaliplatin + capecitabine.

* = FISH positive/HER-2 3+ subgroup.
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