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SHORT COMMUNICATION

Trastuzumab in Combination with FOLFIRI in Patients with Advanced HER2-Positive Gastro-Esophageal Adenocarcinoma: A Retrospective Multicenter AGEO Study

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Abstract

Background Trastuzumab with fluoropyrimidine and cisplatin is the standard first-line treatment in patients with HER2-positive advanced gastro-esophageal adenocarcinoma. However, there are no safety and efficacy data of trastuzumab with FOLFIRI.

Objective To evaluate safety and efficacy of FOLFIRI plus trastuzumab in patients with HER2-positive advanced gastro-esophageal adenocarcinoma.

Patients and Methods This retrospective multicenter study included all consecutive patients with HER2-positive advanced gastro-esophageal adenocarcinoma treated with FOLFIRI plus trastuzumab between 2012 and 2015.

Results A total of 33 patients (median age, 60.3; performance status 0–1, 78.8%) with HER2-positive advanced gastro-esophageal adenocarcinoma treated with FOLFIRI plus trastuzumab in first (n = 3), second (n = 20) or third (n = 10) line of chemotherapy were included. There was one case of a severe non-hematological adverse event corresponding to a left ventricular systolic dysfunction. The most common hematological grade 3 or 4 adverse events were neutropenia (12.9%) and thrombocytopenia (6.4%). There was no febrile neutropenia. For patients treated with FOLFIRI plus trastuzumab in second-line chemotherapy, the median overall survival was 9.5 months.

Conclusions This is the first western population-based study of FOLFIRI plus trastuzumab reporting a satisfactory safety profile and a potential efficacy in advanced HER2-positive gastric cancer.

Key Points

Trastuzumab in combination with cisplatin-based chemotherapy is a validated first-line treatment in patients with advanced HER2-positive gastric cancer. However, to our knowledge, there are no safety and efficacy data of trastuzumab with FOLFIRI

Our cohort study of 33 patients with advanced HER2-positive gastric cancer reported that trastuzumab plus FOLFIRI has a satisfactory safety profile and potential efficacy in second-line treatment after failure of first-line trastuzumab plus platinum-based chemotherapy

This strategy of trastuzumab beyond progression deserves further validation in randomized clinical trials.

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1 Introduction

Trastuzumab is a monoclonal antibody able to bind and prevent cleavage of the extracellular domain of the human epidermal growth factor receptor 2 (HER2). The antitumor effect of trastuzumab is based on the stimulation of antibody-dependent cellular cytotoxicity and the inhibition of the HER2-mediated signaling pathway [1]. Human epidermal growth factor receptor 2, also known as CerbB-2 or ERBB2, is a proto-oncogene that plays a central role in the carcinogenesis of some human tumors. In advanced gastric cancer, the HER2 overexpression that accounts for approximately 10% to 30% of tumors [2] constitutes a predictive marker of response to trastuzumab. The randomized phase III ToGA trial showed in HER2-positive advanced gastric or gastro-esophageal junction (GEJ) adenocarcinoma, a significant improvement in progression-free survival (PFS) and overall survival (OS) with the addition of trastuzumab to chemotherapy including cisplatin and capecitabine or 5-fluorouracil (5FU) (median OS: 13.8 versus 11.1 months; HR 0.74, 95% CI 0.60–0.91; $P = 0.005$) [3]. The survival benefit of trastuzumab was stronger in the HER2-positive subgroup with immunohistochemistry (IHC) 3+ or IHC 2+/ fluorescence in situ hybridization (FISH) positive tumors (median OS: 16.0 versus 11.8 months; HR 0.65, 95% CI 0.51–0.83) [3]. Therefore, based on these results, trastuzumab in combination with fluoropyrimidine and cisplatin became the standard of care for patients with HER2-positive tumors defined as IHC3+ or 2+/FISH positive [4].

For the treatment of HER2-positive gastric or GEJ cancer, trastuzumab has been exclusively developed in combination with platinum salts and fluoropyrimidine drugs. The possibility of combining trastuzumab with other drugs is interesting in some contexts where platinum salts are not the preferred option because of limiting toxicities (i.e., renal failure or neuropathy), or early recurrence after adjuvant therapy based on platinum salts. Furthermore, some targeted therapies have proven effective in continuation treatment after first progression, such as bevacizumab in metastatic colorectal cancer [5] or trastuzumab in HER2-positive advanced breast cancer [6]. However, for patients with HER2-positive gastric cancer, there is no evidence supporting continuation of trastuzumab after failure of first-line platinum-based chemotherapy. So there is an unmet need to evaluate trastuzumab in combination with drugs other than platinum salts in HER2-positive gastric cancer treatment.

The main regimens of chemotherapy used in the treatment of advanced gastric cancer are based on fluoropyrimidines, platinum salts (cisplatin or oxaliplatin), epirubicin, taxanes (docetaxel or paclitaxel), and irinotecan drugs [4]. A randomized phase III study has shown that leucovorin plus 5FU and irinotecan (FOLFIRI regimen) was as effective as epirubicin, cisplatin, and capecitabine (ECX regimen) in first- and second-line treatment in terms of PFS and OS [7]. In this study, the FOLFIRI regimen used in first-line was associated with a better safety profile and a significantly longer time to treatment failure as compared with ECX [7]. Furthermore, in patients with adequate performance status (PS), irinotecan alone used in second or third-line treatment was associated with an improvement in OS and quality of life compared with best supportive care alone [8, 9].

Thus, irinotecan could be an interesting partner with trastuzumab since it can be used in the first- or second-line of chemotherapy for advanced gastric cancer treatment. In addition, preclinical models of gastric cancer cell lines have suggested a potential synergetic antitumor effect between irinotecan and trastuzumab [10, 11]. However, to our knowledge, very little clinical data exists on safety and efficacy of the combination of trastuzumab with irinotecan-based chemotherapy. Therefore, in this current study, we evaluate the efficacy and safety profile of the FOLFIRI regimen combined with trastuzumab in treatment of HER2-positive advanced gastric or GEJ adenocarcinoma.

2 Patients and Methods

2.1 Patients

This retrospective multicenter study included all consecutive patients with histologically proven HER2-positive advanced (locally advanced or metastatic) gastric or GEJ adenocarcinoma who received FOLFIRI in combination with trastuzumab between April 2012 and November 2015 in 13 French centers. The HER2-positive tumor was defined as IHC 3+ or IHC 2+/ FISH positive. This study was reviewed and approved by the Pitié Salpêtrière Hospital ethics committee (CPP Ile-de-France, Paris VI), and performed in accordance with the Declaration of Helsinki and its later amendments.

2.2 Treatment and Outcome

The FOLFIRI plus trastuzumab protocol was administered as follows: biweekly simplified LV5FU2 regimen [12] plus irinotecan (180 mg/m^2), combined with trastuzumab at 6 mg/kg on day 1 of the first cycle, then at 4 mg/kg every 2 weeks. Chemotherapy was continued until disease progression or limiting toxicity occurred. Toxicity was evaluated according to the National Cancer Institute's common toxicity criteria (version 4.0). Tumor response was assessed in patients with measurable disease based on RECIST criteria (version 1.1) [13]. Relevant clinical and tumor characteristics, toxicity, tumor response, and survival status at the last follow-up were collected. The data were updated in June 2016.

2.3 Statistical Analyses

Baseline clinical and pathological characteristics were described as means, median, and range for continuous variables, and frequencies and percentages for qualitative variables.

Overall survival was defined as the time elapsed from the start of the second-line chemotherapy until death (from any causes). Alive patients were censored on the last follow-up date. Survival curves were drawn according to the Kaplan-Meier method. Median follow-up was calculated with the reverse Kaplan-Meier method.

Statistical analyses were carried out using SAS software version 9.4 (SAS Institute, Cary, NC, USA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Patient Characteristics

A total of 33 patients (median age, 60.3; male, 78.8%) with HER2-positive advanced gastric or GEJ adenocarcinoma treated with FOLFIRI plus trastuzumab were included in this study. The ECOG PS was 0–1 for 26 (78.8%) patients. Thirty-one (93.9%) patients had metastatic disease and 15 (45.5%) had two or more metastatic sites. The primary tumor site was located in the GEJ in 23 (69.7%) patients. The FOLFIRI plus trastuzumab regimen was administered in the first (n = 3; 9.1%), second (n = 20, 60.6%) or third (n = 10, 30.3%) line of chemotherapy. The other patient characteristics are listed in Table 1. All patients who received FOLFIRI plus trastuzumab in the second-line regimen were treated with trastuzumab plus a platinum-based regimen in first-line chemotherapy.

3.2 Safety

All but three (missing data) patients were assessable for toxicity. The incidences of hematologic and non-hematologic toxicities are listed in Table 2. There was one case of a severe non-hematological adverse event corresponding to a left ventricular systolic dysfunction (grade 3). The most common hematological grade 3 or 4 adverse events were neutropenia (12.9%) and thrombocytopenia (6.4%). There was no febrile neutropenia. Treatment was discontinued in two patients due to limiting toxicities, the first one after 12 cycles in first-line therapy because of cardiac function deterioration, and the second one after 11 cycles in second-line chemotherapy due to the occurrence of grade 4 neutropenia. There was no death related to the treatment.

3.3 Efficacy

The efficacy of FOLFIRI plus trastuzumab was evaluated in patients who received this regimen in second-line treatment.

Table 1 Clinical and pathological characteristics

	Overall population n = 33 (%)
Age (years)	
Mean	57.4
Median [range]	60.3 [16.3–85.3]
Gender	
Male	26 (78.8)
Female	7 (21.2)
ECOG performance status	
0–1	26 (78.8)
≥2	4 (12.1)
Unknown	3 (9.1)
Primary tumor site	
Gastro-esophageal junction	23 (69.7)
Stomach	10 (30.3)
Histological type	
Intestinal	18 (54.5)
Diffuse or mixed	6 (18.2)
Other or unknown	9 (27.3)
Tumor grade	
Well and moderately differentiated	20 (60.6)
Poorly differentiated	9 (27.3)
Unknown or missing	4 (12.1)
Extent of disease	
Locally advanced	2 (6.1)
Metastatic	31 (93.9)
Measurable disease	
No	3 (9.1)
Yes	30 (90.9)
Number of metastatic sites	
0–1	18 (54.5)
≥2	15 (45.5)
HER2 status	
IHC 3+	29 (87.9)
IHC 2+/FISH positive	4 (12.1)
Line of chemotherapy	
First-line	3 (9.1)
Second-line	20 (60.6)
Third-line	10 (30.3)

Abbreviations: *IHC, immunohistochemistry; FISH, fluorescence* in-situ *hybridization*

3.3.1 Tumor Response

Among the 20 patients treated with FOLFIRI plus trastuzumab in second-line chemotherapy, 17 were assessable for the tumor response (three had no measurable disease). There was one patient with complete response (CR) and two with partial response (PR). The objective response rate (CR and PR) was 17.6%.

Table 2 Toxicity for the combination of FOLFIRI plus trastuzumab in advanced HER2-positive gastro-esophageal adenocarcinoma

	Grade 1 or 2	Grade 3 or 4
Neutropenia	19.3%	12.9%
Febrile neutropenia	0%	0%
Anemia	38.7%	0%
Thrombocytopenia	16.1%	6.4%
Vomiting	22.6%	0%
Diarrhea	38.7%	0%
Mucositis	38.7%	0%
Hand-foot syndrome	12.9%	0%

Percentage of main toxicities are reported for 30 patients (missing data for three patients)

3.3.2 Overall Survival

The median OS from the start of second-line chemotherapy was 9.5 months (95% CI, 4.5–23.0) (Fig. 1). The 1-year OS rate was 49.7% (95% CI, 23.1–71.7).

4 Discussion

To our knowledge, this is the first western population-based study to report the safety and efficacy of FOLFIRI plus trastuzumab in patients with advanced HER2-positive gastric or GEJ cancer. Indeed, data concerning the combination of irinotecan-based chemotherapy with trastuzumab in patients with HER2-positive gastric cancer are lacking, even in the context of patients with other HER2-positive tumors. Our study suggests that FOLFIRI in combination with trastuzumab is well tolerated without any unexpected toxicity. Three patients received FOLFIRI plus trastuzumab in first-line treatment because of contraindications to platinum salt treatment (n = 2) or early recurrence after platinum salt-based adjuvant chemotherapy (n = 1). Interestingly, in the subgroup analysis of the ToGA randomized study, the addition of trastuzumab to fluoropyrimidine and cisplatin was associated with less (or no) survival benefit in patients who had received adjuvant chemotherapy (HR = 0.96; 95% CI, 0.39–2.33) versus those who had not received previous chemotherapy (HR = 0.73; 95% CI, 0.59–0.91) [3]. In case of early recurrence after platinum-based adjuvant chemotherapy, the trastuzumab in combination with drugs other than platinum salts may be an interesting alternative therapeutic option.

In order to assess the benefit of continuation trastuzumab beyond progression, we evaluated the efficacy of FOLFIRI plus trastuzumab as second-line treatment after failure of first-line platinum-based chemotherapy plus trastuzumab. In a recent large retrospective study including 104 patients with disease progression after trastuzumab-containing platinum-based therapy, our group have observed that changing chemotherapy with continuation of trastuzumab was associated with improvement of PFS and OS [14]. As already validated in HER2-positive advanced breast cancer, this strategy of trastuzumab beyond progression in HER-positive advanced gastric cancer deserves to be validated by a randomized study. In the present study, the interesting results in terms of OS suggest a probably synergistic effect between FOLFIRI and

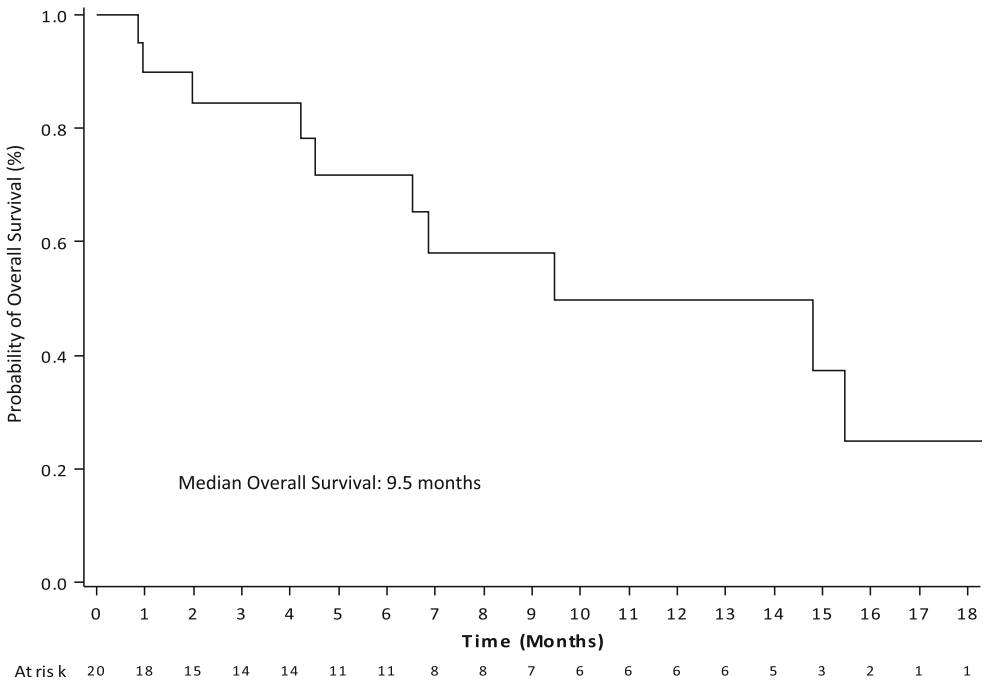

Fig. 1 Kaplan-Meier curve of overall survival from the start of second-line chemotherapy with FOLFIRI plus trastuzumab in patients with HER2-positive advanced gastro-esophageal adenocarcinoma

trastuzumab. However, even if OS is a validated endpoint of efficacy for the second-line treatment of gastric cancer, our results should be interpreted with caution due to the lack of data on PFS (missing data). Furthermore, the relative longer OS observed from the second-line chemotherapy might also be explained by the fact that 11 (55%) patients received a third-line chemotherapy consisting of taxane alone (n = 2) or associated with trastuzumab (n = 4), platinum-based chemotherapy plus trastuzumab (n = 2), ramucirumab alone (n = 1) or associated with taxane (n = 1), and taxane plus carboplatin (n = 1).

As previously mentioned, there is very little data on the efficacy of FOLFIRI with trastuzumab in treatment of patients with HER2-positive gastric cancer. We found two case reports in the literature suggesting an interesting efficacy of FOLFIRI plus trastuzumab, with long survival (more than 8 months) in two pretreated patients with HER2-positive advanced gastric cancer [15, 16]. In the Chinese study published by Sun et al., 34 patients with HER2-positive advanced gastric cancer were randomized to receive either FOLFIRI alone or with trastuzumab [17]. In this study, the overall response rate was significantly higher in patients treated with FOLFIRI plus trastuzumab than FOLFIRI alone (58.8% vs 35.3%). However, no data on grade 3–4 toxicities were available in this article. Furthermore, no indication was given regarding whether patients had received previous chemotherapy and/or trastuzumab before enrollment. In the Japanese phase II study presented in 2016, the authors evaluated efficacy and safety in 29 patients with advanced HER2-positive chemotherapy refractory gastric cancer treated with irinotecan and trastuzumab [18]. The median PFS and OS were 3.7 and 7.5 months, respectively. The major grade 3–4 adverse events were hematological (neutropenia, 24%; anemia, 24%; leucopenia, 21%). Recently, Li et al. evaluated the efficacy of trastuzumab beyond progression in a prospective observational cohort of 59 Chinese patients with HER2-positive advanced gastric cancer [19]. This study showed that continuing trastuzumab in combination with chemotherapy versus chemotherapy alone was associated with an improvement of PFS, while tumor response rate and OS were not significantly improved [19]. Of the 32 patients who continued trastuzumab in second-line treatment, only five received trastuzumab in combination with irinotecan-based chemotherapy. Efficacy and safety data for this subgroup of patients were not specifically reported.

In contrast to HER2-positive breast cancer, trastuzumab remains the only anti-HER2 therapy validated in HER2-positive gastric cancer. The randomized phase III GATSBY trial has compared T-DM1 versus taxane in second-line treatment of patients with HER2-positive tumors defined by IHC3+ or IHC2+/FISH positive. This study did not show a superiority of T-DM1 over taxane in terms of PFS and OS [20]. Further elucidation of HER2 biology is needed to better understand the mechanisms leading to trastuzumab sensibility or resistance in order to identify the patients who would benefit from continuation of trastuzumab beyond progression.

In conclusion, this is the first western population-based study reporting the feasibility of FOLFIRI in combination with trastuzumab in patients with advanced HER2-positive gastric or GEJ cancer. This combination treatment was well tolerated without any unexpected toxicity. The results suggested a potential efficacy of FOLFIRI plus trastuzumab in second-line treatment. This strategy of trastuzumab beyond progression deserves to be validated in a randomized clinical trial.

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Compliance with Ethical Standards

Funding None.

Conflict of Interest Dr. Zaanan has participated in consulting or/and advisory boards for Merck, Amgen, Roche, Sanofi and Lilly; Dr. Taieb has participated in consulting or/and advisory boards for Roche, Sanofi, Merck, Amgen, Baxalta, Celgene, Lilly, Servier, Sirtex.

The remaining authors declare no conflicts of interest.

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