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Case Report

# Elderly Gastric Cancer Locally Advanced with Amplification HER2-When Targeting Therapy Improves Quality of Life

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**Abstract**

Gastric cancer with overexpression of HER2 benefits as well as breast cancer from treatment with trastuzumab. We present the case of an elderly patient with a dysphagia clinic and after deciding that due to frailty and age he was not a candidate for surgical treatment, he maintained a clinical response after more than 6 months with trastuzumab monotherapy while maintaining a good quality of life.

We need new scales to assess the attitude and risk derived from surgery and chemotherapy in an increasingly prevalent population, since well-tolerated drugs such as trastuzumab achieve a clinical benefit in a patient who 6 months ago was unable to swallow.

**Keywords:** Gastric cancer; Trastuzumab; Breast cancer

## Introduction

Up to 30% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2, c-erbB2), and HER2 positivity is associated with significantly worse outcomes than HER2-negative breast cancer [1]. Over the last decade, trastuzumab has revolutionized the treatment of HER2-positive breast cancer and improved its outcomes. With increasing understanding of the molecular biology of HER2, and the availability of genomics and proteomics analyses, it has now been recognized that HER2 is implicated in other severe forms of cancer, notably gastric cancer based in To GA trial as later on we will discuss [2]. HER2 is a proto-oncogene encoded by ERBB2 on chromosome 17. Its major role in these tissues is to promote cell proliferation and suppress apoptosis, which may facilitate excessive/uncontrolled cell growth and tumorigenesis [3].

Because of differences in the examination method and objective criteria, the frequency of HER2- positive gastric cancer varies considerably between studies, ranging from 6.0 to 29.5% in earlier studies. In an effort to address these inconsistencies, the investigators in the ToGA trial conducted a validation study to assess the immunohistochemistry (IHC) and Fluorescence In Situ Hybridization (FISH) protocols for testing HER2 status in advanced gastric cancer and HER2 status was defined as positive (IHC 3 or IHC 2 and FISH-positive) based on the surgical or biopsy specimen staining patterns [4].

Thus, in a scenario where, as in breast cancer, we have a targeted therapy, we will detail a case with a very good response to treatment with the objective of later shedding the evidence of anti HER2 treatment and the importance of assessing individually the patients without excluding treatments solely on the basis of age.

## Case Presentation

An 86-year-old patient who attended a Digestive Consultation due to a picture of epigastralgia, weight loss of 8 kg, and asthenia. Dysphagia to solids, well tolerated liquids (turmix diet). Intestinal habit every 48 hours.

No recent income as a personal history, only hypertension stands out. Independent for the basic activities of daily life.

The following complementary tests are carried out:

### Gastroscopy 20/04/2018

Esophagus: Morphology and normal folds.

In the esophagus immediately supracardial there is a vegetating, ulcerated formation of infiltrating-malignant aspect, affeccting approximately 30% of the circumference, lightly closing the light but allowing the passage of the endoscope.

The lesion extends distally, also affecting the cardia and the subcardial area that presents deep ulceration.

Biopsy lesion of distal esophagus and cardia: infiltrative adenocarcinoma. Immunohistochemical study to determine overexpression of C-erb-B2 protein with which observe an INTENSE MEMBRANE POSITIVITY (+++ / +++).

### Thoraco-abdominal CT 04/05/2018

No nodular lesions are identified in the lung parenchyma.

There are no significant mediastinal, hilar or axillary adenopathies.

There is a discrete thickening of the walls of the gastric fundus, adjacent to the cardia, with small adjacent regional adenopathies. No liver metastasis.

### Ecoendoscopy (09/05/2018)

At about 42 cm in what corresponds to the cardiac area, semicircunferential thickening of the layers begins, which begins in the mucosa and extends to rupture the muscularis propria and invade




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the adventitia with respect to separation planes with neighboring aorta organs and diaphragmatic pillars. Several perilesional images were observed at least 5 hipoecogénies rounded between 4 and 8 mm suggestive of pathological adenopathies, no adenopathies in the celiac trunk or hepatic hilus or aorto-cava space. Uncinate, head, body and tail of pancreas of normal structure and morphology. Cholecystectomized. No liver metastases.

### Diagnosis

Cardiac neoplasia uT3N2Mx.

### Tumoral markers ( 06/06/2018)

Carcinoembryonic antigen (C.E.A.) 3.3 ng/ml (0.0 - 5.0), CA 19-9 antigen 567.0 U/ml (0.0 - 37.0).

With the diagnosis of cardiac adenocarcinoma uT3N2Mx with overexpression of HER2, the case is presented in the Tumor Committee deciding not surgery due to age and high surgical risk. Given that its main symptomatology is dysphagia, prostheses are placed on June 20, 2018.

He is reassessed at 2 weeks in the Oncology Consultation, maintaining a good general condition and tolerating the túrmix diet. Given that it maintains ECOG and it is a patient> 80 years, with objective of symptomatic control, we decided CAPECITABINE 1000 mg/m$^2$ scheme every 12 hours x 14 days + TRASTUZUMAB 8 mg/kg 1$^s$t cycle, followed by 6 mg / kg, with the idea of administering 6 cycles followed by Trastuzumab maintenance.

Chemotherapy starts with a dose of Capecitabine 1500 mg for breakfast and dinner (body surface 1.6). However, at 10 days, he presented chest pain of 2 hours evolution, oppressive type with elevation of cardiac markers (maximum troponin of 0.259µg/L) without alterations in electrocardiogram. Assessed by Cardiology, they can not rule out acute coronary syndrome without ST-segment elevation, so they start antiaggregation with Aspirin, nitroglycerin patch and simvastatin.

During admission, a clear tumor response was observed, with mobilization of the prosthesis, which is located inside the stomach.

Gastroscopy is repeated for prosthesis removal and little residual tissue is observed.

Given that capecitabine may have contributed to vasospasm and risk again to produce a cardiac event in a frail patient, we suspended capecitabine and given the good response with only 1 cycle of treatment, we decided to continue with trastuzumab.

Echocardiogram without alterations.

Assessed again in Consulta, maintains very good general condition, without new cardiac events after discharge. On July 19, the 2$^{nd}$ cycle of trastuzumab monotherapy was scheduled, without complications.

Valued again on August 9, refers clinical improvement, allowing passage of non-crushed food. Tumor markers in descent, with CEA at normal limit: 2.3 ng/ml (0.0 - 5.0), and CA 19.9 201 U/ml when the diagnosis was 567.

TC September after 5th cycle, in full response. Continues with full response in TC December 2018.

## Discussion

The ToGA trial was a prospective, phase 3, open-label trial in which patients with HER2-positive advanced gastric or gastroesophageal junction cancer were randomly allocated to receive either trastuzumab in combination with chemotherapy or chemotherapy alone [2]. Chemotherapy was given every 3 weeks for six cycles. Trastuzumab was administered at a dose of 8 mg/kg on day 1 of the first cycle and then at 6 mg/kg every 3 weeks until disease progression, unacceptable toxicity, or withdrawal of consent. Finally, 584 patients received study treatment and were analyzed. The general characteristics of patients in both groups were similar, including age (59.4 *vs.* 58.5 years), chemotherapy regimen (capecitabine and cisplatin: 87 *vs.* 88%; fluorouracil and cisplatin: 13 *vs.* 12%), and primary tumor site (stomach: 90 *vs.* 83%; gastroesophageal junction: 20 *vs.* 17%). Overall, 97% of patients in both groups had metastatic disease at study entry.

The primary endpoint of the study was overall survival, which was defined as the time from randomization to death from any cause, showing in patients receiving trastuzumab plus chemotherapy an increase of 2.7 months in median overall survival [13.8 *vs.* 11.1 months and Progression-free survival (6.7 *vs.* 5.5 months)

The overall response rate in the trastuzumab plus chemotherapy group was 47% (complete response: 5%; partial response: 42%) and was significantly greater than that in the chemotherapy-alone group (35%; complete response: 2%; partial response: 33%) [2].

However, as we see, no older patients included, mostly compared with cisplatin and 5FU and metastatic ones. In a setting where older patients are increasing, we recommend new studies with older patients to see if toxicity differs.

Another point to discuss is the evidence of monotherapy with antiHER2( Toga trial compares chemo vs chemo + antiHER2, not only antiHER2).Trastuzumab monotherapy is used as maintenance therapy for patients with breast cancer based on the study by Vogel et al, who reported an objective response rate of 26%. Kaplan–Meier analysis showed that 1 year of trastuzumab maintenance therapy was associated with significantly greater disease-free survival (85.8 *vs.* 77.4%; and distant recurrence-free survival (90.6 *vs.* 82.8%) compared with observation alone with a median follow-up of 1 year [5].

In gastric cancer, to expand these breast cancer findings of trastuzumab monotherapy, a pilot study was conducted in which patients who progressed while on chemotherapy for metastatic or locally advanced HER2- positive gastric cancer were treated with trastuzumab monotherapy.However, the study only involved four patients; therefore, additional studies are needed to confirm the potential of trastuzumab monotherapy [6].

In TOGA trial, only 8% stopped chemo because of adverse event, so we do not have many data of what happens in this population who do not receive the optimal treatment.Continuation of trastuzumab after discontinuation of chemotherapy likely contributed to the prolonged survival in the trastuzumab plus chemotherapy group. However we do not know if the Benefit is the same thant with chemo or if in frail patients like ours, even not starting chemo would be a good option.

As this is not a common entity, there are only a few cases reported, which responds after 47 cycles trastuzumab and 6 cycles of chemo [7].

Finally, and related with older patients, new trials with only elderly patients would be ideal but this population with her2 would have a very slow enrollment. We will need some scales assessing surgical and chemotherapy risk as Hurria or PACE scales to avoid chemo or even perform a gastrectomy if patient is fit [8].

Future questions could be: what will happen at the progression? The survival advantage of second-line chemotherapy was recently confirmed in a German study comparing irinotecan *vs.* best supportive care for gastric cancer and in a South Korean study comparing salvage chemotherapy (docetaxel or irinotecan) plus best supportive, but new trials with immunotherapy are now the most important so enrollment in Her2 trials is more difficult [9]. Probably breast cancer will give us some clues in a near future.

## Conclusions

1. The targeted treatment antiHER2 is an effective target, safe and with very good results in gastric cancer with overexpression

2. New studies are needed to help us assess the benefit of chemotherapy added to antiHER2 in frail patients

3. In elderly patients, assessment in the form of scales and multidisciplinary management is the key to choosing the best treatment

4. Many questions about the benefit of maintaining the target treatment to the progression as well as the optimal time in patients who do not undergo surgery with curative intent.

5. Needing of biomarkers.

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