



# Plasma levels of trastuzumab in gastric cancer: Case report

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## Abstract

**Introduction:** The use of trastuzumab with a fluoropyrimidine and platinum compound is currently the standard first-line treatment of patients with metastatic HER2-positive gastric cancer, but it appears that serum levels of trastuzumab determine the clinical effectiveness of this treatment, affecting progression-free survival and overall survival.

**Case report:** We report the case of a patient with metastatic HER2-positive gastric cancer, receiving XELOX (fluoropyrimidine and oxaliplatin) plus trastuzumab at standard doses, who presented sub-therapeutic serum levels during the first two treatment cycles and rapid disease progression (progression-free survival = 5.6 months).

**Discussion:** This case reveals a possible cause of poor effectiveness of trastuzumab treatment for metastatic gastric cancer in some patients, namely low circulating levels of the drug. It highlights the importance of monitoring as a possible tool for individual dose adjustment to optimize this therapy.

## Keywords

Trastuzumab, gastric cancer, pharmacokinetics

## Introduction

Although the incidence of gastric cancer (GC) has decreased considerably in recent decades,<sup>1</sup> it remains the third leading cause of cancer-related deaths worldwide.<sup>2</sup> This is mainly because most cases of GC are diagnosed with advanced stages of the disease<sup>3</sup>; when diagnosed at initial stages, surgery and adjuvant chemotherapy are often curative.

Regarding the molecular biology of this tumor, around 23% of cases of GC overexpress the HER2 membrane receptor,<sup>4</sup> which is a negative prognostic factor. Overall survival (OS) of patients with HER2-positive GC is around 5.5 months compared to 12.6 months for patients without over-amplification of this membrane receptor.<sup>5</sup> Thus, this receptor has been identified as a potential therapeutic target, by trastuzumab. This was demonstrated in the treatment of HER2-positive GC in the ToGA trial, where the addition of trastuzumab to platinum compound and fluoropyrimidine<sup>5</sup> (fluorouracil or capecitabine) in naïve patients showed a significant improvement in OS, especially in cases with high levels of HER2 expression (IHC 3+ on immunohistochemistry), 16 vs. 11.8 months (HR 0.65

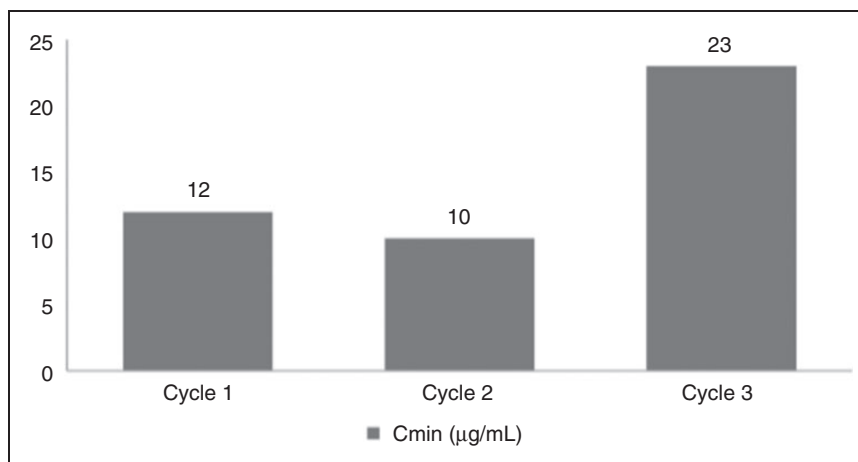
(95% CI 0.51–0.83)).<sup>6</sup> On the basis of these findings, the regimen of trastuzumab with 5-fluorouracil or capecitabine and cisplatin or oxaliplatin has become the standard first-line treatment for patients with HER2-positive GC. However, HER2 suppression has not proved as satisfactory as expected. In the ToGA trial, the overall response rate with the addition of trastuzumab was less than 50%.<sup>6</sup> A possible explanation for these poor results is low plasma levels of the drug during treatment in some patients. Mean plasma concentrations of trastuzumab in patients with GC are 24–63% lower than those found in patients with breast cancer when used at the same dose.<sup>7</sup> The clinical implications of this lower exposure are now known, as

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**Figure 1.** Minimum plasma concentrations at the first three cycles of trastuzumab.

recently shown by Yang et al.,<sup>8</sup> who described that patients included in the ToGA trial, with minimum plasma concentrations ( $C_{\min}$ ) below 11.4 µg/mL in the first cycle, showed worse progression-free survival (PFS) and OS than patients who with higher plasma concentrations of trastuzumab.

In this paper, we describe the plasma concentrations of trastuzumab and clinical response to treatment shown by a patient diagnosed with metastatic HER2-positive GC.

### Case report

A 48-year-old man, weighing 82 kg, with hypertension, dyslipidemia, alcoholism and former smoker, was admitted after two months of symptoms including dyspepsia, epigastric pain, and vomiting. Gastroscopy showed an ulcerated infiltrating tumor measuring approximately 70 × 64 mm in the antrum that compressed the pylorus (Borrmann III). Computed tomography (CT) revealed the presence of multiple thoracoabdominal hypodense lesions involving both hepatic lobes, most of them in the segment 8–5, with maximum transverse diameters of approximately 12 × 10.4 cm, confirming the diagnosis of advanced GC (stage IV) and an initial ECOG of 0. On 22 July 2015, antineoplastic treatment was initiated with EOX<sup>9</sup> (epirubicin 50 mg/m<sup>2</sup> day 1, oxaliplatin 130 mg/m<sup>2</sup> day 1 and capecitabine 625 mg/m<sup>2</sup>/12 h day 1 to 21). Three weeks later, histopathology of tumor samples obtained during gastroscopy confirmed that it was a tumor overexpressing HER2 (FISH technique > 6 signals/cell, immunohistochemistry IHC 3+), which prompted therapeutic change to treatment with XELOX (capecitabine 1000 mg/m<sup>2</sup>/12 h day 1 to 14, oxaliplatin 130 mg/m<sup>2</sup> day 1) plus trastuzumab (6 mg/kg every three weeks, with initial loading dose of 8 mg/kg).<sup>10</sup>

Plasma levels of trastuzumab were determined just before administration of each dose ( $C_{\min}$ ), as from the second administration of the drug, using ELISA in accordance with the manufacturer's specifications (SHIKARI<sup>®</sup> Q-TRAS).<sup>11</sup> Trastuzumab  $C_{\min}$  levels were below 20 µg/mL after administration of the first two cycles of chemotherapy (12.3 mg/mL and 10.1 µg/mL, respectively). It was not until the third administration of trastuzumab that the  $C_{\min}$  exceeded 20 µg/mL (23.2 µg/mL) (Figure 1).

After two months of treatment, thoracoabdominal CT scan showed a partial response with a decrease in the size of the antrum-pyloric mass as well as the size and number of liver metastases. Despite this early response after four cycles, a new CT scan (December 2015) confirmed disease progression with an increase in pyloric antrum-mass and liver metastases. This prompted a change to second-line treatment with paclitaxel-ramucirumab. Thus, trastuzumab was associated with PFS of 5.6 months.

### Discussion

This paper describes the case of a patient diagnosed with metastatic HER2-positive GC treated with XELOX and trastuzumab. Despite presenting favorable predictors of response (male, ECOG 0, measurable tumor lesions, HER2 overexpression ICH3 +) the patient showed rapid disease progression. The patient did present a PFS of 5.6 months, which is comparable to that shown by the group of control patients in the ToGA study (5.5 months). In our case, the addition of trastuzumab did not provide all the clinical benefit expected of it. We believe the poor response may be attributable to the low plasma concentrations of the drug in the first two cycles (12.3 and 10.1 mg/mL, respectively). This is based on the fact that the

minimum therapeutic concentration of trastuzumab necessary to block all HER2 receptors is considered to be 20 µg/ml.<sup>12,13</sup> A first dose of 8 mg/kg iv or 600 mg subcutaneous trastuzumab has been established as necessary to ensure a  $C_{\min}$  of at least 20 µg/ml.<sup>14</sup> In many cases, these levels are not achieved in patients with GC, as in the present case. In fact, for HER2-positive GC patients, higher initial doses of trastuzumab are currently being investigated in an ongoing international phase III trial, comparing the current dose (6 mg/kg every three weeks with an initial loading dose of 8 mg/kg) versus 8 mg/kg every three weeks, with an initial loading dose of 10 mg/kg (the HELOISE study).<sup>15</sup> While awaiting the publication of results, we wished to add to existing information about the relationship between levels of trastuzumab in HER2-positive GC patients and clinical response to treatment. The present case also suggests that monitoring plasma levels of trastuzumab could be a potential tool to optimize treatment by individual dose adjustment.

#### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

#### Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

#### Supplemental material

All supplemental material mentioned in the text, is available in the online version of the journal at <http://opp.sagepub.com/supplemental>

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