Case Report

The Effectiveness of Trastuzumab Combined with Sequential Chemotherapy for Metastatic Gastric Carcinoma with Overexpression of HER2

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Keywords

Adenocarcinoma · Chemotherapy · Trastuzumab

Abstract

Metastatic gastric carcinoma is a mortal disease with a median survival of barely 10 months. An approximate 20% of the cases overexpress HER2, and among them, the combination of chemotherapy with trastuzumab is actually the first-line palliative treatment. However, after progression, sequential strategies of chemotherapy while maintaining trastuzumab have been barely researched. We report the case of a patient with a diagnosis of adenocarcinoma in the gastroesophageal junction with overexpression of HER2, in stage IV, treated with sequential chemotherapy and trastuzumab, who survived more than 5 years during the metastatic phase maintaining a good quality of life.

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Introduction

Metastatic gastric carcinoma is a mortal disease with a median survival of barely 10 months. An approximate 20% of the cases overexpress the epidermal growth factor receptor 2 (HER2), and among them, the combination of chemotherapy with trastuzumab is actually the first-line palliative treatment because of the proved increase of survival versus chemo-

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therapy alone (ToGA Study). However, sequential strategies of chemotherapy while maintaining trastuzumab have been barely investigated.

We introduce the case of a patient with metastatic gastric carcinoma overexpressing HER2, who was treated with sequential monotherapy in association with trastuzumab, surviving more than 5 years with a good quality of life.

Case Report

A 75-year-old man presented with a neoplasm in the gastroesophageal junction.

On December 2009, he underwent a total esophagectomy, a gastropasty, and a pyloroplasty. It was a well-differentiated adenocarcinoma of 7 cm with free resection margins. A total of 6 perigastric lymph nodes (2 metastatic ones), 2 paraesophageal lymph nodes (no metastasis), and 6 subcarinal lymph nodes (no metastasis) were removed.

At that time, the patient was asymptomatic with no pathological signs after objective examination, and was classified as T2N1M0 after cancer staging classification. He received chemotherapy adjuvant with ptegafur, a 400-mg dose p.o. every 12 h on days 1–21 within a 28-day cycle for 6 months with good tolerance.

In a routine examination carried out in May 2011 while the patient was asymptomatic, a thorax-abdomen computed tomography (CT) scan showed metastatic relapse at a lung level (several node images, the biggest ones being 12 × 11 mm in the upper lobe in the left hemithorax and 9 × 8 mm in the right hemithorax); the rest of the tests carried out (general analysis, CA 19.9, and esophagogastroduodenoscopy) showed no alterations. An immunohistochemical study (IH) was requested to evaluate the overexpression of HER2 in the primary tumor piece and it was positive (IH 3+). Furthermore, the left ventricular ejection fraction was established at 70.9% (lower limit of normal: 55%).

On June 2011, he started first-line palliative chemotherapy with capecitabine at doses of 1,000 mg/m² p.o. every 12 h on days 1–14 within 21-day cycles, in association with trastuzumab since the first cycle, at doses of 8 mg/kg weight the first time and thereafter at doses of 6 mg/kg weight i.v. every 21 days. After receiving 25 cycles, during which he remained stable according to response evaluation criteria in solid tumors (RECIST guidelines), a CT scan performed on November 2012 showed progression of the disease at a lung level plus a potential malignant adenopathy in the left hilum of the lung. CA 19.9 showed 50 U/ml (normal range: 2–37), and the rest of the parameters in the analysis were within the normal values. Because of the long duration of the stabilization of the disease we decided to continue with the second-line chemotherapy treatment in association with trastuzumab.

The patient received the following lines of chemotherapy while maintaining the same doses of trastuzumab: oxaliplatin 130 mg/m² i.v. every 21 days (11 cycles), docetaxel 70 mg/m² i.v. every 21 days (5 cycles), irinotecan 200 mg/m² i.v. every 21 days (24 cycles), carboplatin (area under the curve 5) i.v. every 21 days (6 cycles), paclitaxel 80 mg/m² i.v. every 7 days (6 cycles), and paclitaxel 175 mg/m² i.v. every 21 days (7 cycles).

In all cases, the change to the next line of treatment was made by progression of the disease, as the toxicity did not prevent the treatment from continuing its course.

The toxicities, following the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE-v4.0), were grade 2 asthenia in the 18th cycle of capecitabine together with a moderate decrease of creatinine clearance (44.5 mL/min) (therefore the capecitabine dose was reduced 25%), grade 1 peripheral neuropathy since the 1st cycle of oxaliplatin, and grade 2 anemia in the 4th cycle of docetaxel (which caused a decrease in the dose of 50%).

The left ventricular ejection fraction was not altered during the whole treatment, showing final figures of around 77.3%.

During the whole evolution, the patient did not show symptoms or signs of disease, maintaining a performance status of 0 according to the Eastern Cooperative Oncology Group (ECOG) scale until his death in November 2016 due to a respiratory infection.

Discussion

Gastric carcinoma is the third cause of death associated with neoplasms in both genders. Worldwide incidence is 17.4 and 7.5 cases per 100,000 people in the male and female population, respectively, showing a mortality rate per 100,000 people of 12.7 in the male population and 5.7 in the female population [1]. Treatment of the advanced diseased with chemotherapy leads to a slight increase of survival, with medians below 1 year [2].

Around 20% of gastric neoplasms overexpress HER2 [3], and the combination of chemotherapy (cisplatin and/or fluoropyrimidines) with trastuzumab (humanized monoclonal antibody IgG1 which acts at HER2 level) is considered the first-line treatment in advanced diseases. This is based on the results of the ToGA study, a phase III randomized clinical trial which included 584 patients with gastric or gastroesophageal junction adenocarcinoma in locally advanced or metastatic stage with overexpressed HER2 (defined as IH 3+ or positive fluorescence in situ hybridization) and who had not received treatment for advanced disease previously. The results showed a significant increase of response rate (47 vs. 35%), median of progression-free survival (6.7 vs. 5.5 months) and overall survival (13.8 vs. 11.1 months) in comparison to chemotherapy alone [4].

Disease progression in general implies resistance to treatment, which is the result of the genetic instability related to cancer, but this concept cannot be applied to biological agents that could provide a better prognosis of the disease by maintaining the anti-target drug after progression [5].

Two phase III randomized trials analyzed the effectiveness with other anti-HER2 in second-line treatment. The GATSBY trial analyzed the effectiveness of trastuzumab-emtansine (T-DM1) versus taxanes in patients with advanced HER2+ gastric carcinoma previously treated with trastuzumab [6]. The TyTAN trial [7] analyzed the effectiveness of lapatinib with paclitaxel versus chemotherapy alone (in this trial only 15 patients had received trastuzumab before). Both trials concluded that adding those anti-HER2 drugs to second-line chemotherapy did not improve survival.

Some articles concerning the effectiveness of trastuzumab in second-line treatment have been published. These are series with a low number of patients and clinical case descriptions [8–11], although most patients had not received previous treatment with trastuzumab. Only 1 study [9] evaluated the efficacy of trastuzumab in patients who had previously progressed to chemotherapy in association with trastuzumab. However, all the data seem to suggest a good effectiveness with adequate toxicity, and some authors believe that a longer duration of exposure to trastuzumab might reduce the risk of death by advanced gastric carcinoma [8].

Recently, a retrospective multicenter trial reported on patients with advanced gastric or gastroesophageal junction adenocarcinoma in advanced situation and overexpressing HER2, who progressed to a first-line treatment with chemotherapy and trastuzumab. If we compare the group of patients who received a second-line treatment of chemotherapy with trastuzumab to those who did not receive trastuzumab in progression, we can see an in-

crease both in progression-free survival (4.4 vs. 2.3 months) and overall survival (12.6 vs. 6.1 months) [12].

The survival of patients with advanced gastric carcinoma usually does not reach 1 year, therefore improving that number is still a challenge. Rebischung et al. [11] described a case treated with several lines of chemotherapy combined with trastuzumab who reached a survival of around 4 years, similar to our case. On the other hand, it does not seem that trastuzumab adds much toxicity to that already expected according to the chemotherapy provided. Therefore, although scarce, data seem to suggest that prolonging the treatment with trastuzumab might improve the results achieved with chemotherapy.

In the case explained, the patient was an old man in general good health, therefore we opted for a first-line treatment with capecitabine-trastuzumab. After noticing the stabilization of the disease for 18 months, we considered that the blocking of HER2 might have been key in the duration of the response, so the treatment was continued with monotherapy and trastuzumab, modifying chemotherapy at each progression of the disease. Monotherapy was generally well tolerated in our case, and the low toxicity allowed the patient to maintain a good quality of life until his death (survival in metastatic stage of 66 months).

Among all the drugs given to the patient, those which stabilized the disease during the longest time were capecitabine (indicated in first-line treatment) and irinotecan (indicated in fourth-line treatment), with a stabilization of 18 months each. We must take into account that, despite not having obtained response of the disease to treatment, the patient did not show any symptom derivate of it during its evolution and reached longer than expected survival for this type of pathology.

In conclusion, we believe that the sequential treatment of chemotherapy while maintaining trastuzumab and modifying cytostatics according to the progression of the disease is a strategy that should be researched in patients suffering from metastatic gastric neoplasm with overexpression of HER2.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

No sponsorship or funding was received for this study. The authors have no conflicts of interest to declare.

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