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Feasibility of intraperitoneal Trastuzumab treatment in a patient with peritoneal carcinomatosis from gastric cancer

M. BERRETTA[1,2], R. FISICHELLA[3], E. BORSATTI[4], A. LLESHI[1], S. IOFFREDO[1], N. MENEGUZZO[5], V. CANZONIERI[6], A. DI GRAZIA[7], R. CANNIZZARO[8], U. TIRELLI[1], S. BERRETTA[3]

[1]Department of Medical Oncology, National Cancer Institute, Aviano, Italy
[2]Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy
[3]Department of Surgery University of Catania, Catania, Italy
[4]Nuclear Medicine Service, National Cancer Institute, Aviano, Italy
[5]Division of Cardiology, National Cancer Institute, Aviano, Italy
[6]Divison of Pathology, National Cancer Institute, Aviano, Italy
[7]Division of Radiotherapy, REM Center, Catania, Italy
[8]Divison of Gastroenterology, National Cancer Institute, Aviano, Italy

Abstract. – OBJECTIVES: This case report evaluates the feasibility and efficacy of intraperitoneal (IP) trastuzumab administration in gastric cancer (GC) patients with peritoneal carcinomatoses.

METHODS: Peritoneal metastasis is a common sign of advanced tumor stage, tumor progression or disease recurrence in patients with GC. Recently, the role of HER2 overexpression in GC, occurring in about 20% of cases, is correlated with a worse prognosis. We report the case of 61-years old female, admitted to our Hospital after curative surgery for GC with over-expression of HER2. Seven months after the start of first line chemotherapy treatment a pleuro-peritoneal disease progression occurred, documented by cytological exam; according to HER2 status, we decided to treat the patient with IP trastuzumab administration.

RESULTS: Between September and October 2012, the patient (ECOG performance status was 0), underwent to 6 cycles of IP trastuzumab. Trastuzumab was administered weekly at a dose of 150 mg for each cycle after paracentesis.

The safety was good, no local complications (e.g. abdominal pain, peritonitis) occurred. The clinical revaluation evidenced a stable peritoneal disease.

CONCLUSIONS: To our knowledge this is the first report on Trastuzumab use to treat IP metastases from GC, with acceptable toxicity and local disease control.

Key Words:
Gastric cancer, Trastuzumab, Peritoneal carcinomatosis, Chemotherapy, Treatment.

Introduction

Although the incidence of gastric cancer (GC) has decreased during the past years, it remains the fourth most common newly diagnosed cancer worldwide and the second leading cause of cancer-related death[1-4]. Peritoneal carcinomatosis (PC) is a common sign of advanced tumor stage, tumor progression, or disease recurrence in patients with GC[4]. In a previously published retrospective analysis of 1172 patients with GC after R0 resection, the peritoneal recurrence rate was 29%, and the median time from recurrence at any location to death was 6 months[5]. This tumor manifestation was mostly associated with a poor prognosis.

More than 15 years ago, c-ErbB-2 (HER2) expression in GC was found to be correlated with a more differentiated subtype, and also with a worse prognosis[7]. The incidence of HER2 overexpresion in GC occurs in about 20% of case[8]. In the trastuzumab for Gastric Cancer study (ToGA), 594 HER2-positive patients with GC were randomized in first-line therapy. The study demonstrated that targeting HER2 with trastuzumab in addition to standard chemotherapy significantly improves the overall survival (OS) of patients. The major benefit occurred in the group of patients with immunohistochemistry (IHC) 3+ or IHC 2+ with fluorescence in situ hybridization (FISH) positivity, with a median overall survival greater than 16 months[9].

Corresponding Author: Massimiliano Berretta, MD, Ph.D; e-mail: mberretta@cro.it

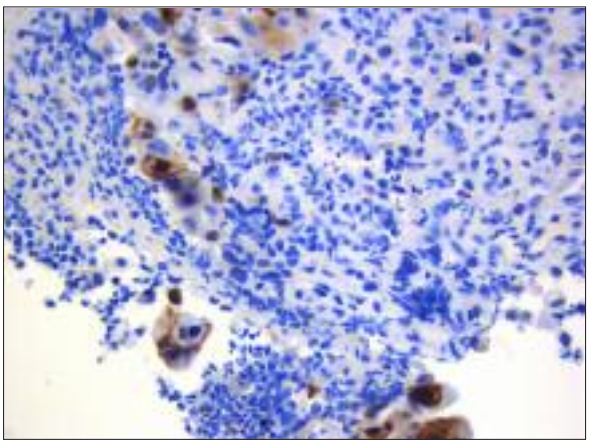

Figure 1. Primary gastric adenocarcinoma immunopositive for HER2 (score 3+) (4B5) O.M. 20x, Hematoxylin-counterstain.

To date no data are available on the use of trastuzumab in the treatment of PC for HER2+ GC.

However, we report, for the first time, the results achieved on a patient with GC who received intraperitoneal (IP) trastuzumab for the treatment of PC.

Case Report

In December 2011 a 60-year old woman was submitted to gastrectomy with D2 lymph node resection in stage pT4a N3b(17/26) M0, G3, intestinal type gastric adenocarcinoma. By immunohistochemical analysis, cancer cells were positive for HER2 (score 3+) (Figure 1). In January 2012, the patient was admitted to the Aviano National Cancer Institute to start antiblastic chemotherapy (AC) for metastatic GC. She did not present with relevant comorbidities and the ECOG Performance Status was 0. The peri-operative staging, documented by computed tomography and bone scan, was negative for visceral and/or bone metastases. Between January and April 2012 she was treated with Trastuzumab/Folfox-regimen[10,11]; therapy was well tolerated except for Oxaliplatin. In fact, from March 2012 the treatment continued without Oxaliplatin due to a laryngospasm and a dysphonia adverse event[12]. In May 2012 the CT scan evaluation was negative for relapse of disease and, considering the high risk to develop local recurrence disease, she underwent radiotherapy treatment (50.4 Gy deliverd in fractions of 1.8 Gy per day), with concomitant capecitabine administration as radiosensitivity. The treatment was complicated by G2 diarrhea approached with symptomatic treatment. In August 2012 a pleuro-peritoneal disease progression was documented by increased levels of Ca 19.9 serum marker (385 U/mL), thorax and abdomen CT scan, and citologic exam on pleuric and periotoneal fluid resulted positive for metastasis from GC. In the light of this event, the patient underwent systemic AC with trastuzumab[12] and intrapleuric (IPL) weekly cisplatin administration (60 mg for cycle), obtaining a complete pathologic response on pleuric site, and a stable disease on peritoneal site. The decision to treat the patient with IPL Cisplant on the pleuric site was based on more English literature evidence and due to the symptomatic disease in that site. Between September and October 2012, considering the excellent response obtained by IPL local treatment, documented by cytologic IP fluid exam and on the basis of abdominal ultrasound scan (USC), and the HER2 status (+), as determined by immunocytochemical analysis performed on paraffin embedded cell-block sections, obtained from peritoneal fluid (Figure 2), we decided to administer IP trastuzumab, excluding the use of Cisplatin, due to a moderated increased level of creatinine serum. The treatment consisted in a weekly IP trastuzumab administration at total dose of 150 mg for each cycle, administered in 1 hour after the systemic administration of corticosteroids and antiemetic therapy to prevent abdominal pain and nausea/vomiting. The treatment was well tolerated and no local and systemic adverse events occurred. The heart function was evaluated every 2 weeks with electrocardiography and every month with echocardiography. After the

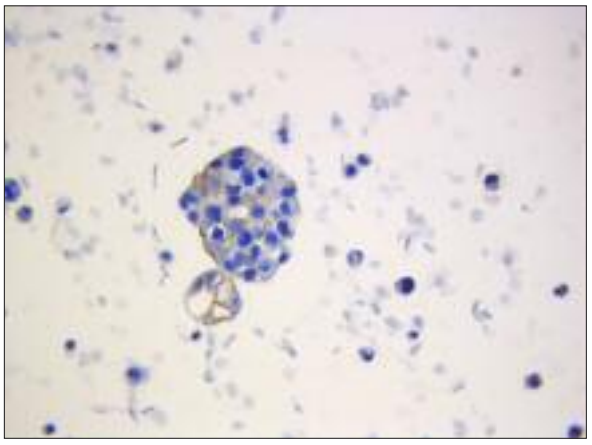

Figure 2. Peritoneal fluid cancer cells immunopositive for HER2. O.M. 20x, Hematoxylin-counterstain.

sixth cycle of IP trastuzumab treatment the USC showed a SD, abdominal pain (due to peritoneal carcinomatosis), was reduced and the Ca 19.9 serum level was stable. The toxicity profile was good and in particular no cardiologic toxicities were evidenced. Considering the good tolerance of IP treatment and the patient's good clinical conditions, we decided to restart with systemic AC folfox4-regimen, previous oxaliplatin desensibilitation, obtaining a dramatical decrease of Ca 19.9 serum level and a SD documented by thorax and abdomen CT-scan. In December 2012 a new progression of disease was documented and the patient died one month later due to rapid progression of metastatic disease on the liver.

Discussion

Trastuzumab is a monoclonal antibody against the extracellular domain of the HER2 receptor[9]; it has significantly increased the OS (more than 16 months for patients with HER2 over expression) in the treatment of metastatic GC (ToGA trial).

We have reported, for the first time, the safety of IP trastuzumab administration in a patient with PC by GC. Some authors reported on the use of intratecal trastuzumab in leptomeningeal metastases from breast cancer and the results were good, especially for safety[13,14].

Our decision to treat this patient (who had previously received IPL cisplatin as local treatment) with IP trastuzumab was based on previous experiences and has evidenced good results in terms of local disease control. Unfortunately we could not use IP cisplatin due to a moderate increased level of creatinine serum level. The rationale to use IP trastuzumab, was derived from some considerations: first of all the encouraging results obtained in other studies[13,14] in the treatment of leptomeningeal carcinomatosis from breast cancer; second, HER2 antigen positivity of primary gastric and peritoneal fluid adenocarcinoma cells; third, the scarce efficacy of AC systemic treatment for peritoneal carcinomatosis, and finally, the strong motivation of the patient to exploit the opportunity of IP treatment with target therapy. No data existed on the use and adequate dosing and frequency of IP trastuzumab, but we considered the schedule used in the treatment of leptomeningeal carcinomatosis by breast cancer.

Conclusions

This case report illustrates that the administration of IP trastuzumab is feasible and safe, and able to obtain a good clinical abdominal pain control. We suggest to evaluate the use of trastuzumab in the treatment of PC in patient with GC and HER2 over expression, even if further studies are necessary to better understand which is the correct timing to use this drug, and probably better results could be derived from a more adequate selection of patients.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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