

CLINICAL VIGNETTE

Trastuzumab based Neoadjuvant chemotherapy for Locally Advanced HER2 Over Expressing Gastric Adenocarcinoma

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Abstract

A 75-year-old Japanese male with a history of intermittent right upper quadrant abdominal pain was found to have a HER2 overexpressing locally advanced gastric adenocarcinoma involving the distal stomach and infiltrating the right paramedian abdominal wall. He underwent neoadjuvant chemotherapy with trastuzumab, capecitabine, and cisplatin for four cycles. A staging PET-CT fusion study revealed partial response, allowing for partial distal gastrectomy with extensive D2 lymph node dissection. Following surgery an additional four cycles of trastuzumab, capecitabine and cisplatin were given. Patient has remained free of disease recurrence to date. This case illustrates the benefit of neoadjuvant trastuzumab based chemotherapy in the management of HER2 overexpressing gastric adenocarcinoma.

Key Words: Gastric Adenocarcinoma; HER2; Neoadjuvant chemotherapy; Trastuzumab

Introduction

Gastric cancer is the fourth most commonly diagnosed malignancy globally and is the second leading cause of death from cancer. Surgery remains the primary treatment modality for patients with localized disease. Unfortunately, survival of these patients remains low (20 to 50%) and as a result, there is a need for more effective perioperative therapies¹. Recently, a monoclonal antibody targeting HER2 has been utilized in management of patients with gastric cancer². Here we report the outcome of a patient receiving neoadjuvant trastuzumab based chemotherapy for locally advanced gastric cancer and review the literature.

Case Report

A 75-year-old Japanese male with a past medical history significant for gout and cholecystectomy presented with complaints of intermittent right upper quadrant abdominal pain for several months. Upper endoscopy revealed a friable circumferential 4 cm

mass as well as ulceration in the distal body of the stomach. Pathology was consistent for a moderately differentiated adenocarcinoma of signet ring type in a background of *Helicobacter Pylori* infection. Fluorescent in-situ hybridization (FISH) testing for HER2/neu (HER2) gene amplification was positive at HER2/CEP17 ratio of 6.7

Patient underwent staging computed tomography (CT) scan of chest abdomen and pelvis which was notable for a 5 cm ill-defined mass in the distal stomach which infiltrated the right paramedian abdominal wall closely marginating the under surface of the left lobe of the liver with minimal surrounding inferior mesenteric fat stranding. A positron emission tomography-CT (PET-CT) fusion study revealed an ovoid mass lesion originating from the gastric antrum associated with intense FDG activity and CT evidence for omental infiltration with no regional adenopathy. Due to the locally advanced nature of the tumor, patient was started on neo-adjuvant chemotherapy with capecitabine (1000 mg/m² orally twice a day for fourteen days), cisplatin (80 mg/m² on day 1 every three weeks, and trastuzumab (8mg/kg on day 1 of first cycle and 6 mg/kg on day of each subsequent cycle every three weeks). Patient tolerated the chemotherapy, noting only grade 2 fatigue, and grade 1 diarrhea. Following four cycles of chemotherapy, staging PET-CT fusion study revealed a partial response with some interval decrease in the size of the mass in the anterior aspect of the antrum [Figure 1]. However there was persistent concentric wall thickening with infiltration into the adjacent omentum and persistent increased metabolic activity. Patient was subsequently taken to surgery and underwent partial distal gastrectomy with extensive D2 lymph node dissection. Surgical pathology evaluation confirmed a residual moderately differentiated gastric adenocarcinoma of the intestinal type, which was 2.3 cm in size. Excision margins were all negative; however there was evidence for peri-neural and lympho-vascular microscopic invasion. Metastatic adenocarcinoma was seen in one out of the sixty-seven excised lymph nodes, consistent with T3N1M0 (Stage IIIA) disease. Post-operative course was uneventful. An additional four cycles of chemotherapy with

cisplatin, capecitabine, and trastuzumab were given post surgery. Routine follow-up imaging with PET-CT fusion studies up to 28 months post surgery have not revealed any evidence for disease recurrence.

Discussion

HER2 over expression has been previously described in esophagogastric cancers with a prevalence ranging from 15 to 27%³⁻⁵. HER-2 is a tyrosine kinase receptor, which plays a key role in signal transduction, cell growth and maturation⁶. Several trials had shown a negative correlation between HER2 over-expression and prognosis in gastric carcinoma⁷⁻¹¹. In addition, In vitro experiments in gastric cell lines as well as in vivo experiments in xenograft mice models have both demonstrated that blockade of HER2 receptor can result in tumor regression¹². Trastuzumab, a monoclonal antibody against HER2, has exhibited antitumor activity in HER2 over-expressed gastric cancer cells^{13, 14}. For example, it has been demonstrated that trastuzumab can enhance the cytotoxic effects of ahracyclines in HER2 amplified gastric cells, and suppress proliferation of the gastric cells in xenograft models^{15, 16}.

Such preclinical work resulted in several Phase II clinical trials looking specifically at incorporation of trastuzumab with chemotherapy regimens in patients with advanced gastric cancer. One phase II trial of 22 patients with advanced gastric cancer and HER2 over expression receiving trasztuzumab and cisplatin had a confirmed overall response rate of 32% and median time to progression of 5.1 months¹⁷. Another Phase II trial assessed the activity of trastuzumab, cisplatin and docetaxel therapy in patients with metastatic gastric or gastroesophageal junction cancer with HER2 overexpression. In the initial presentation of the five treated patients, there was one complete response, three partial response and one stable disease (disease control rate of 100%)¹⁸. The promising activity in the Phase II setting resulted in the design of the Phase III ToGA trial.

The ToGA trial was an open-label international, phase 3 randomized trial of 594 patients with inoperable locally advanced, or metastatic adenocarcinoma of stomach or Gastro-esophageal junction that were HER2 positive by FISH or with 3+ IHC. Of the 584 evaluable patients only 20 had inoperable localized disease and 564 had metastatic disease. The trial randomized patients between trastuzumab in combination with capecitabine plus cisplatin or fluorouracil chemotherapy versus chemotherapy alone. At the median follow up of 18.6 months, The trastuzumab and chemotherapy arm was associated with an increase in response rate ((47.3% versus 34.5%), an increase in median progression free survival (6.7 versus 5.5 months) and an increase in median overall survival (13.8 versus 11.1 months). This study has established trastuzumab chemotherapy

combination as the standard of care for patients with HER2 positive, metastatic esophagogastric cancer¹⁹.

In patients with localized, potentially resectable gastric adenocarcinoma long-term outcomes are suboptimal with surgery alone, and we currently do not have a true standard of care for adjuvant or neo-adjuvant therapy. Multimodality treatment strategies are currently preferred in the medically fit patients. Multiple, small trials have shown efficacy of induction chemotherapy followed by chemoradiation or chemoradiation alone prior to surgery, but, none have been widely adopted as a standard²⁰⁻²³. The largest and most influential trial in this setting has been the MAGIC trial²⁴. This trial randomized more than 500 patients to surgery alone versus perioperative chemotherapy (three cycles of triplet chemotherapy prior to surgery, and three cycles post surgery). Radiation was not used in these patients, and overall survival was significantly improved in the group that received chemotherapy. According to the National Comprehensive Cancer Network (NCCN) guidelines this regimen has been given a category 1 recommendation for patients with resectable T2 or higher cancers.

Despite the number of trials demonstrating benefit of trastuzumab in addition to chemotherapy in unresectable or metastatic esophagogastric cancer, there has been no trial looking at the role of trastuzumab in the neoadjuvant setting. A review of literature found only two other case reports utilizing trastuzumab-containing regimen in a neoadjuvant fashion. In one report, neoadjuvant regiment containing trastuzumab, oxaliplatin, docetaxel and capecitabine for three cycles resulted in complete pathological response²⁵. In another report, neoadjuvant chemotherapy using trastuzumab, oxaliplatin and capecitabine resulted in partial response by imaging and successful resection of the primary gastric tumor²⁶. In both cases, patients received an additional three cycles of chemotherapy following the definitive surgery. Our case above represents a third example where trastuzumab based neoadjuvant chemotherapy resulted in successful resection of the primary HER2 over-expressing localized gastric cancer and is the only reported case of utilizing combination of trastuzumab, capecitabine and cisplatin in a neoadjuvant setting. In addition, with more than 24-month follow-up, our patient has remained disease free by imaging and is completely asymptomatic. Taken together, these three case reports are intriguing and suggest that there may be clear role for trastuzumab based neoadjuvant chemotherapy in treatment of localized gastric adenocarcinoma and perhaps this combination warrants further exploration in a clinical trial setting.

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Figure Legend

Figure 1: PET-CT fusion study done approximately two months post initial imaging demonstrating partial response with interval decrease in the size of the mass in the anterior aspect of the antrum denoted by the arrow.

