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CASE REPORT

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Aggressive HER2-Positive Gastric Cancer in a Young Patient, Refractory in Trastuzumab and Progressive with Trastuzumab-Emtansine Treatment

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Abstract

Gastric cancer remains a major global health problem. Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths in the world. The prognosis of the disease is poor because it is often diagnosed at later stages, especially at HER2-positive. Most patients diagnosed with gastric cancer present with advanced, incurable disease. This report details the case of a 30-year-old male patient diagnosed with metastatic gastric adenocarcinoma. Stage T3 N3 M1, PD-L1 0%, and HER2+. The patient was administered neoadjuvant palliative chemotherapy, eight cycles of FLOT, and the last two cycles of HER-FLOT. The patient constantly had elevated levels of liver enzymes, and therefore, endoscopic retrograde cholangiopancreatography with biliary stenting was performed. After chemotherapy followed by restaging, the tumor board, based on the findings, decided to remove the primary tumor from this young patient. The operation was performed as a palliative da Vinci-assisted total gastrectomy with lymphadenectomy. Then, trastuzumab monotherapy was prescribed. At that time, the patient's follow-up with PET-CT showed progression with hypermetabolic lymph nodes in the paraaortic and aortocaval regions, as well as left hydronephrosis. As a result, we started the second-line therapy with T-DM1, an antibody-drug conjugate trastuzumab-emtansine (KADCYLA), for five cycles. At the time of receiving the sixth cycle, the patient's condition changed dramatically due to liver and heart problems, pleural effusion, and bleeding. After two years of treatment, all oncological-specific therapies have been ended, and the patient has been put in palliative care to relieve suffering and to support the best possible quality of life.

This case underlines the importance of identifying potential therapeutic targets and developing therapies to improve the outcomes of systemic treatment beyond those currently achieved with conventional chemotherapy and targets.**(International Journal of Biomedicine. 2024;14(1):187-192.)**

Keywords: gastric cancer • HER2 resistance • trastuzumab

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Abbreviations

HER2, human epidermal growth factor receptor 2; **IHC**, immunohistochemistry; **NTRK**, neurotrophic tropomyosin-receptor kinase; **OS**, overall survival.

Introduction

Gastric cancer remains a major global health problem. Gastric cancer is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related deaths in the world.[1,2] The prognosis of the disease is poor because it is often diagnosed at later stages, especially at HER2-positive.[3-10] Over 95% of gastric cancers are adenocarcinomas.[11]

Overexpression of the HER2 protein or amplification of the *ERBB2* gene has been implicated in the development of gastric adenocarcinoma.[12] Some studies suggest that HER2 positivity is associated with poor prognosis.[5-10] In contrast,

others have shown that it is not an independent prognostic factor of patient outcome, except in a very small subgroup of patients with intestinal histology.[13-15] The reported rate of HER2 positivity in patients with gastric cancer ranges from 12% to 23%,[6,7,14,15] and in Europe, it is less than or equal to 20%. HER2 positivity was significantly higher in males than in females.[16]

Chemotherapy remains the standard care treatment approach for patients with advanced-stage disease; however, response rates are relatively low, and the prognosis is poor, with a median survival of only 8–10 months. Trastuzumab, in combination with chemotherapy, in the first-line setting of patients with metastatic, HER2-positive gastric cancer, represents the first targeted therapeutic method to demonstrate improvement in response rate and survival in gastric cancer. However, not all patients with HER2-positive gastric cancer respond to trastuzumab, and most patients who do initially benefit from trastuzumab develop resistance to it. Treatment with trastuzumab is based on the presence of HER2 overexpression.[16]

Case Presentation

A 30-year-old male patient with a family history unremarkable for gastric cancer was diagnosed with gastric cancer stage T3N3M1, along with multiple pathologically enlarged retroperitoneal lymph nodes, multiple small mediastinal lymph nodes, peritoneal carcinomatosis, ascites, and strong suspicion of osteolytic skeletal metastases without cortical erosion. Gastroscopy was performed with biopsies in July 2021. It showed histologically as gastric adenocarcinoma, partly solid and poorly differentiated G3, PD-L1 expression negative, NTRK IHC negative, and HER2 positive.

The patient was administered neoadjuvant palliative chemotherapy, eight cycles of FLOT, and the last two cycles of HER-FLOT. The patient constantly had elevated levels of liver enzymes, and therefore, endoscopic retrograde cholangiopancreatography with biliary stenting was performed. In December 2021, after chemotherapy followed by restaging, the tumor board, based on the findings, decided to remove the primary tumor from this young patient. Restaging shows a very good remission endoscopically and in the abdominal CT scan. The operation was performed as a palliative da Vinci-assisted total gastrectomy with lymphadenectomy. The findings in post-operative histopathology according to UIUCC-TNM classification (8th Edition, 2017): cT1b pN0(0/10) LO VO Pn0. Regression grade <10%. Then, trastuzumab monotherapy was prescribed until May 2023. At that time, the patient's follow-up with PET-CT showed progression with hypermetabolic lymph nodes in the paraaortic and aortocaval regions, as well as left hydronephrosis (Image 1).

As a result, we started the second-line therapy with T-DM1, an antibody-drug conjugate trastuzumab-emtansine (KADCYLA), for five cycles. At the time of receiving the sixth cycle, the patient's condition changed dramatically due to liver and heart problems, pleural effusion, and bleeding.

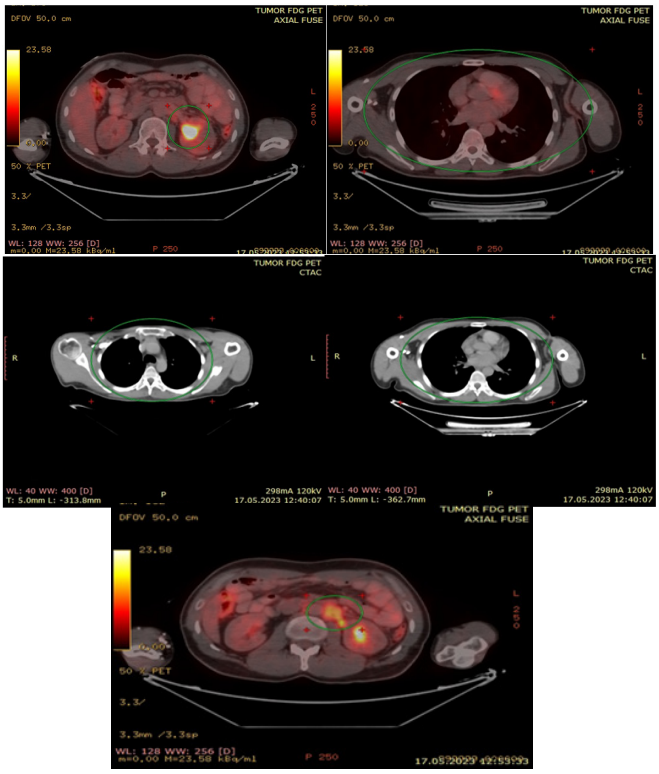
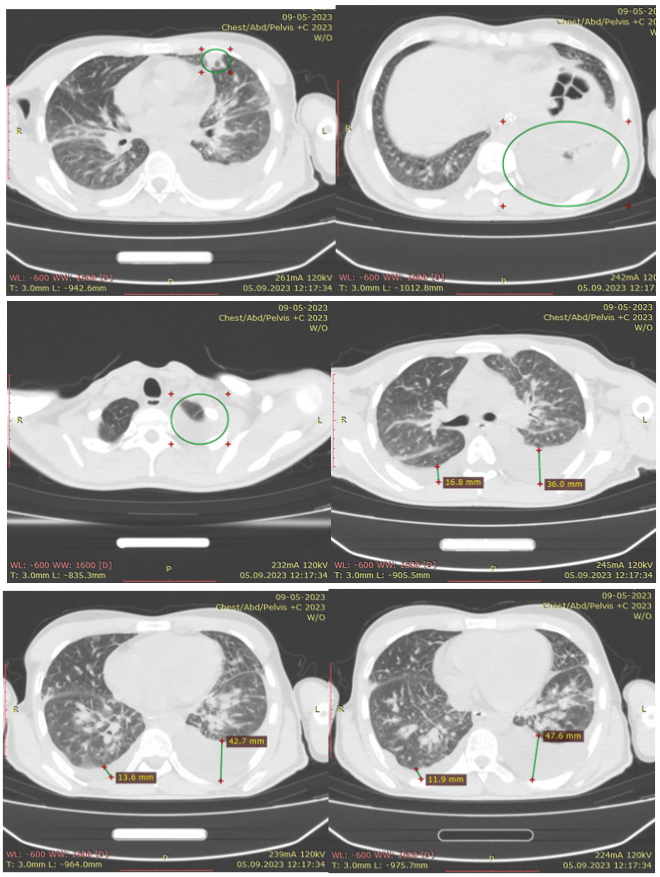


Image 1. *PET-CT evaluation during Trastuzumab treatment (May 2023).*

The chest CT scan detected a pleural effusion up to 5 cm in the left lung and 1.5 cm in the right lung, lesions in the pericardiac area, and the left lung parenchyma (Image 2).



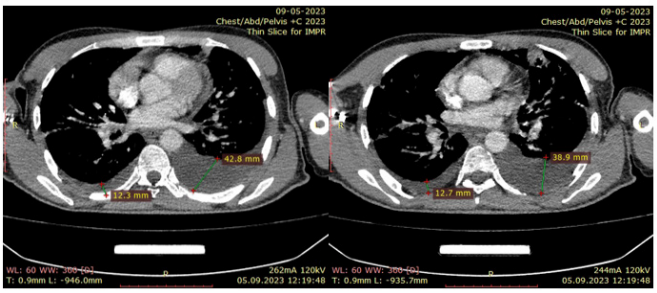


Image 2. *Chest CT scan (September 2023).*

So, after two years of treatment, all oncological-specific therapies have been ended, and the patient has been put in palliative care to relieve suffering and to support the best possible quality of life. He pursued many multidisciplinary interventions to relieve major symptoms, resulting in the prolongation of life.

Discussion

Gastric cancer represents a conglomerate of histologically and biologically heterogeneous diseases, which are characterized by various genomic alterations that result in activating molecular pathways. We know more about the biological behavior of gastric cancer and its intrinsic subtypes, particularly the *ERBB2* amplified gastric cancer subtype. HER2+ is implicated with poor prognosis and aggressiveness of gastric cancer.

Pathologic review and biomarker testing play important roles in gastric cancer diagnosis, classification, and molecular characterization. Classification based on histologic subtype and molecular features helps improve early diagnosis and has implications for therapy.[17] Presently, IHC and/or molecular testing for HER2/*ERBB2* status, MSI or MMR status, tumor mutational burden-high status, and *NTRK* gene fusion are implicated in the clinical management of advanced gastric cancer.[18] PD-L1 testing may be considered on locally advanced, recurrent, or metastatic gastric cancer in patients who are candidates for treatment with PD-1 inhibitors. An FDA-approved companion diagnostic test should be used to identify patients for treatment with PD-1 inhibitors.

Treatment of Gastric Cancer

Trastuzumab is a monoclonal antibody that binds to the extracellular domain of the HER2 receptor, blocking its downstream signaling pathway. It promotes an antibody-dependent, cell-mediated cytotoxicity by activating apoptotic signals in tumor cells.[19] Patients who underwent chemotherapy with cisplatin and fluorouracil in combination with trastuzumab had a better median OS than those who got only chemotherapy (16 months vs 11 months). This is mainly due to the survival advantage of patients with high expression of the HER2 protein.[16,20,21]

Antibody-drug conjugate is an emerging antibody bioconjugate, which is an immunoconjugate composed of a monoclonal antibody bound to a cytotoxic drug through a chemical linker, combining the antigen specificity of the antibody and the potency of the cytotoxic agent at the same time. However, patients with advanced gastric cancer treated with T-DM1 did not have a clear OS advantage over those treated with taxanes.[22,23] The issue has gained attention as most patients develop resistance to trastuzumab. Trastuzumab resistance appears to be primarily mediated by tumor heterogeneity. Treatment failure with anti-HER2 therapy is also associated with changes in receptor tyrosine kinase-RAS-PI3K signaling. To overcome this problem, various new drugs and treatments are emerging.[24,25] Intratumor heterogeneity and genomic instability processes shape tumor evolution in space and time, and growing evidence suggests a link between assessment heterogeneity and poor prognosis. This explains the mismatch between the costs and benefits of some cancer treatments.[26,27]

Surgery is the primary treatment option for patients with localized gastric cancer. Clinical staging using chest/abdominal/pelvic CT scan, with or without endoscopic ultrasound (if no metastatic disease is seen on CT), should be performed before surgery to assess the extent of the disease and degree of nodal involvement.[28]

Combined modality therapy has been shown to significantly increase survival in gastric cancer patients with locoregional disease.[29-31] Perioperative chemotherapy is recommended for localized resectable disease (category 1).[30,32-35]The survival benefit of perioperative chemotherapy in gastric cancer was first demonstrated in the landmark phase III MAGIC trial.[35] In the randomized controlled phase FLOT4 trial, Albatran et al. compared perioperative chemotherapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) to the standard ECF regimen in patients with respectable, non-metastatic gastric or esophagogastric junction adenocarcinoma (≥cT2 and/or N+).[33]

Systemic therapy can provide palliation, improved survival, and enhanced quality of life in patients with locally advanced or metastatic gastric cancer.[36-38]

First-line systemic therapy regimens with two cytotoxic drugs are preferred for patients with advanced disease because of their lower toxicity. The use of three cytotoxic drugs in a regimen should be reserved for medically fit patients with excellent performance status and easy access to frequent toxicity evaluations.[40] Studies have shown that most gastric cancer recurrences occur within the first 2 years after the completion of local therapy (70%–80%), and almost all recurrences occur within 5 years (~90%).[41-43] The selection of regimens for second-line or subsequent therapy is dependent upon prior therapy and performance status.[44]

In conclusion, with the advancement of tumor immunotherapy, combined immune checkpoint inhibitors will emerge as a promising treatment, hopefully resulting in decreased tumor size and improved objective response rates. Intratumor heterogeneity may be the most important primary mechanism of anti-HER2 drug resistance. Patients with refractory HER2-positive status should be put in the new study in combination with chemotherapy and/or immunotherapy or new research approaches to participate in well-designed clinical trials investigating novel therapeutic strategies to enable further advances. Potential loss of HER2 positivity after first-line anti-HER2 treatment requires reexamining HER2 status before initiating second-line anti-HER2 therapy.

To better assess patient outcomes, we need improved diagnostic, prognostic, and disease surveillance methods despite the availability of various treatments. A combination of immunotherapy and anti-HER2 monoclonal antibodies may be required.

Competing Interests

The authors declare that they have no competing interests.

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