Case Report

HER2-Positive Esophagogastric Junction Adenocarcinoma with Lung and Para-Aortic Lymph Node Metastases Treated with Conversion Surgery Following the Administration of a Trastuzumab Containing Chemotherapy Regimen: A Case Report

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Abstract
We report a case of HER2-positive esophagogastric junction adenocarcinoma with multiple lung and para-aortic lymph node metastases in a 40-year-old male patient in whom surgical treatment was successful following the administration of a trastuzumab containing chemotherapy regimen. After esophageal stent placement, a chemotherapy regimen consisting of capecitabine (2,000 mg/m²/day, days 1-14), cisplatin (80 mg/m² day 1), and trastuzumab (during the first course: 8 mg/kg, day 1; second and subsequent courses: 6 mg/kg, day 1) was administered. After six courses, the patient developed renal dysfunction, thus cisplatin was withdrawn and only capecitabine and trastuzumab were administered (every 3 weeks) thereafter. The patient’s metastatic lesions were no longer detected on CT, and the primary tumor showed a partial response for 16 months. Subsequently, the primary tumor began to grow in size. Lung and para-aortic lymph node metastases remained invisible on FDG-PET. Total gastrectomy with D2 lymph node dissection and sampling of the para-aortic lymph nodes was performed. No complications observed after surgery. An R0 resection was achieved. The histological effect of chemotherapy was Grade 1a. Cancer cells from the regrowth of the tumor were HER2-positive. The patient is currently receiving capecitabine as adjuvant chemotherapy. A follow-up CT scan at 6 months after the operation detected no recurrence. The patient remains alive at 8 months after surgery.

Key words: HER2 positive, trastuzumab, conversion surgery

Introduction
Stage IV gastric or esophagogastric junction carcinomas have a dismal prognosis. A number of recent studies have reported the effectiveness of chemotherapy for unresectable advanced gastric cancer including reports of patients who underwent conversion surgery following chemotherapy.¹⁻⁸

Human epidermal growth factor receptor 2 (HER2) was first studied with respect to its role in breast cancer, and it has been found to be an important prognostic factor.⁹⁻¹¹ In gastric and esophageal cancer, the incidence of HER2-positive tumors ranges from 4 to 53% and 9 to 64%, respectively.² The ToGA trial revealed that trastuzumab was effective in the treatment of HER2-positive gastric cancer.¹³ Based on the results of the ToGA trial, trastuzumab-containing chemotherapy has been designated as the standard treatment for HER2-positive recurrent/unresectable advanced gastric cancer in Japan.¹⁴

We herein report a case of HER2-positive esophagogastric junction adenocarcinoma with multiple lung and para-aortic lymph node metastases that was successfully treated by surgery following the administration of a chemotherapy regimen that contained trastuzumab. The results indicate that some patients with HER2-positive Stage IV gastric or
esophagogastric junction adenocarcinoma can undergo conversion surgery following the administration of a trastuzumab-containing chemotherapy regimen.

Case Report
A 40-year-old male patient visited our hospital complaining that he had experienced sensation of his throat being blocked by food during eating for 2 months. At the same time, his body weight decreased by 10 kg. His past and family histories were unremarkable. He had smoked 20 cigarettes a day for 20 years and had drank 500–1,000 ml of beer a day for 20 years. No nodes in the neck area, including Virchow’s node, were palpable. A digital examination did not reveal Schnitzler’s metastasis. Laboratory studies revealed that the patient’s carcinoembryonic antigen (CEA) level was elevated (41.48 ng/ml), but that his CA19-9 level was within the normal range. Neither anemia nor malnutrition was detected. Upper esophagogastrroduodenoscopy showed an irregular bleeding mass, categorized as a type 3 tumor of the esophagogastric junction (Fig. 1). The histological examination of a biopsy specimen from the tumor revealed that it was a moderately differentiated tubular adenocarcinoma. The immunohistochemical examination of a biopsy specimen taken by upper esophagogastrroduodenoscopy revealed that it was HER2-positive. A radiographic contrast study from the esophagus to the stomach showed stenosis from the abdominal esophagus to the gastric cardia of approximately 2.5 cm in length (Fig. 2). CT showed multiple nodular lesions of 2–4 mm in diameter in both lung fields, and that the para-aortic lymph nodes were swollen to 16 mm in diameter (Fig. 3A, B). Based on these findings, the patient was diagnosed with unresectable HER2-positive cancer at the esophagogastric junction with multiple lung and para-aortic lymph node metastases. Chemotherapy was initiated after the placement of an esophageal stent at the stenotic lesion of the esophagus. A chemotherapy regimen consisting of capecitabine (2,000 mg/m²/day, days 1–14), cisplatin (80 mg/m², day 1), and trastuzumab (during first course: 8 mg/kg, day 1; second and subsequent courses: 6 mg/kg, day 1) was chosen. After receiving six courses, the patient developed renal dysfunction due to cisplatin. Thus cisplatin was withdrawn and only capecitabine and trastuzumab were administered (every 3 weeks) thereafter. The patient’s CEA levels returned to the normal range, there was a significant decrease in the size of the tumor at the primary lesion, and the esophageal stent was spontaneously removed from his mouth. The patient’s lung and para-aortic lymph node metastases were not visible on CT. After receiving 21 courses, the patient’s CEA levels gradual-
Conversion surgery for HER2-Positive stage IV gastric cancer

Fig. 3  A CT scan showed multiple nodular lesions in both lung fields (A) and para-aortic lymph node swelling (B). After the administration of a trastuzumab-containing chemotherapy regimen, the patient’s lung and para-aortic lymph nodes metastases became unclear (C, D).

ly increased (7.17 → 8.81 → 11.03 ng/ml over 3 months). CT subsequently showed the enlargement of the primary tumor: however, the metastatic lung and para-aortic lymph nodes remained unclear (Fig. 3C, D); they were also invisible on FDG-PET (Fig. 4). Total gastrectomy with D2 lymph node dissection and para-aortic lymph nodes sampling was performed (Fig.5). No complications were observed after the operation. Histologically, an R0 resection was achieved. Cancer cells were not detected within the sampled para-aortic lymph nodes. The pathological results of the resected specimen were as follows: UE, Less, Type 3; 43 × 28 mm, tub1, ypT3 (SS), int, INFb, ly1, v2, ypN0, pPM (-), pDM0, ypStage II A (Japanese Classification of Gastric Carcinoma, the 14th Edition). The histological effect of chemotherapy was Grade 1a. Cancer cells from the regrowth of the tumor were HER2 positive. The patient is currently receiving capecitabine as adjuvant chemotherapy. A follow-up CT scan at 6 months after the operation detected no recurrence.

Fig. 4  FDG-PET showed the uptake of FDG in the tumor at the esophagogastric junction, but not in either the lung or the para-aortic lymph nodes.
Fig. 5 A surgical specimen showed the regrowth tumor at the esophagogastric junction (A). The specimen was HER2 positive (×50) (B).

He has been alive for 8 months after surgery.

Discussion

Surgery is a key treatment for esophagogastric junction carcinoma. Curative surgical resection is extremely important in terms of improving the survival of patients suffering from advanced esophagogastric junction carcinoma. Thanks to recent advances in chemotherapy, conversion surgery is now possible in patients who are diagnosed with unresectable gastric cancer \(^1\)-\(^5\); however, a search of the PubMed database using the keywords “esophagogastric, HER2 positive, and conversion” yield no English articles about conversion surgery for HER2-positive esophagogastric junction adenocarcinoma with lung and para-aortic lymph node metastases.

Human epidermal growth factor receptor 2 (HER2) protein is a 185-kDa transmembrane tyrosine kinase receptor that is a member of the epidermal growth factor receptor (EGFR) family. It was first discovered in breast cancer. In carcinomas, HER2 acts as an oncogene \(^{15}\). It has been assessed in gastric and esophageal cancer \(^{16,17}\). In gastric and esophageal cancer, the incidence of HER2 positive tumors ranges from 4 to 53% and 9 to 64%, respectively \(^{12}\). In Japan, the incidence of HER2-positive advanced or recurrent gastric cancer is reported to be 21.1\% \(^{16}\). The ToGA trial demonstrated the effectiveness of trastuzumab for HER2-positive gastric cancer \(^{13}\). The administration of a trastuzumab-containing chemotherapy regimen is the standard treatment for HER2-positive recurrent/unresectable advanced gastric cancer in Japan, based on the results of the ToGA trial \(^{14}\). There have been some recent reports on the effectiveness of trastuzumab-containing chemotherapy regimens in the treatment of unresectable advanced gastric cancer \(^{19-21}\).

We experienced a case of HER2-positive esophagogastric junction adenocarcinoma with metastasis to the lung and para-aortic lymph nodes. The patient could only consume liquids due to severe stenosis of the abdominal esophagus. Chemotherapy was initiated after the placement of an esophageal stent. A chemotherapy regimen was administered which consisted of capecitabine (2,000 mg/m\(^2\)/day, days 1-14), cisplatin (80 mg/m\(^2\), day 1), and trastuzumab (during the first course: 8 mg/kg, day 1; second and subsequent courses: 6 mg/kg, day 1). After receiving six courses, the patient developed renal dysfunction as a side effect of cisplatin; thus, only capecitabine and trastuzumab were administered every 3 weeks thereafter. The tumor and multiple lung and para-aortic lymph node metastases showed a remarkable response to the regimen, and allowed the patient to undergo conversion surgery.

The REGATTA trial revealed that gastrectomy had no survival benefit in patient with advanced gastric cancer with a single non-curable factor, especially in the case of total gastrectomy \(^{22}\). As such, chemotherapy with or without molecular target drugs should be chosen for unresectable gastric or esophagogastric cancer if the tumor does not cause...
severe symptoms (such as bleeding and/or stenosis). In our patient, an esophageal stent was placed in order for the patient to eat meals and start chemotherapy. During the placement of an esophageal stent, attention should be paid to complications such as perforation, bleeding, and pneumonia.

In our patient, the esophageal stent was removed from the mouth spontaneously; however, the stent had the potential to cause problems due to the decrease in the size of the primary tumor. Moreover, we should be aware that a rapid decrease in tumor size, which may occur when a malignant tumor of the digestive tract, including the stomach, responds remarkably well to chemotherapy, can lead to perforation, which is one of the most important complications of chemotherapy.

There is currently no consensus on the optimal timing of conversion surgery after chemotherapy in patients with gastric or esophagogastric junction cancer, whether adjuvant chemotherapy is useful, and if it is useful, what types of adjuvant chemotherapy are effective. The answer to these questions should become clear as more cases are investigated in the future.

In conclusion, during chemotherapy in patients suffering with unresectable gastric or esophagogastric junction carcinoma, careful attention should be paid to the side effects of anticancer or molecular-targeted drugs. Furthermore, the therapeutic efficacy should be assessed at appropriate intervals as it is extremely important not to miss the window for performing surgery.

References


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