

Conversion therapy for advanced gastric cancer with trastuzumab combined with chemotherapy: A case report

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Abstract. Gastric cancer is a common cancer of the gastrointestinal tract and the second most prevalent cause of cancer-associated mortality globally. Gastric cancer-associated mortality is increased in China compared with that in other countries. Key contributors to the poor prognosis of gastric cancer include late clinical presentation and genetic heterogeneity. Treatment based on the subtype of gastric cancer is important for effective therapy. The overexpression of the erb-b2 receptor tyrosine kinase 2 (ERBB2) gene and protein is associated with gastric cancer in humans. Chemotherapy and targeted therapy may control tumor growth and recurrence, which is an important function of conversion surgery. The present study reported a patient diagnosed with gastric cancer with multiple abdominal cavity and retroperitoneal lymph node metastases. ERBB2 amplification and overexpression were identified in both case reports presented. The patients were treated with four cycles of oxaliplatin, capecitabine and trastuzumab. Computed tomography revealed the lymph node metastases decreased in size following treatment, and surgical resection was performed. The four cycles of oxaliplatin, capecitabine and trastuzumab were continued subsequent to surgical resection at the administered dose. No recurrence was observed for >1 year after surgery. Trastuzumab combined with oxaliplatin and capecitabine as a conversion therapy regime for ERBB2-overexpressing advanced gastric adenocarcinoma increased the likelihood of successful surgical resection, and prolonged progression-free survival.

Introduction

In China, gastric cancer is the second most common type of cancer in males and the fourth most common type in females (1). The majority of patients with gastric cancer are

diagnosed at the advanced stage, and the prognosis for patients with advanced gastric cancer is poor (2). Surgical resection is a cornerstone gastric cancer treatment, particularly during the early stage (3). Chemotherapy, radiotherapy, targeted therapy, palliative surgery and best supportive care have been used to treat patients with late stage gastric cancer (4). Conversion therapy may be feasible for prolonging overall survival. As gastric cancer is a heterogeneous disease, therapy should be performed based on subtype, and specific biomarkers and different treatment targets ought to be identified for each subtype (5). Erb-b2 receptor tyrosine kinase 2 (ERBB2) overexpression has been reported in 12-27 and 9-23% of patients with gastric cancer according to different studies (6-12). For patients with ERBB2+ gastric cancer, it has been advised that trastuzumab is administered as chemotherapy. The efficacy and safety of trastuzumab were evaluated in the Trastuzumab for Gastric Cancer (ToGA) trial (13), and it has been reported that trastuzumab may be used for conversion therapy (14,15). In the present study, the treatment regimen consisted of trastuzumab combined with oxaliplatin and capecitabine (XELOX), and was performed following surgery. Tumors were resected, conversion therapy was successful, and good clinical outcomes were achieved. Written informed consent was obtained from the patients for the present study and any accompanying images to be published. The Ethics Committee of Sichuan Cancer Hospital (Chengdu, China) approved the present study.

Case reports

Case 1. A 40-year-old female was admitted to Sichuan Cancer Hospital with a complaint of lower back pain for >1 month. An abdominal ultrasound revealed retroperitoneal lymph node enlargement. Gastroscopy revealed a gastric tumor, rough mucosa and a 3 cm ulcer in diameter in September 2013 (Fig. 1). Biopsy revealed a poorly differentiated adenocarcinoma. Immunohistochemical analysis revealed ERBB2 overexpression (Fig. 2) (16). Computed tomography (CT) revealed that multiple lymph nodes were enlarged along the lesser curvature of the stomach, common hepatic artery, head of the pancreas, pancreatic vein, and the postcaval and para-aortic lymph nodes (Fig. 3). The clinical diagnosis was gastric body adenocarcinoma with abdominal cavity lymph node metastasis; the clinical stage was cT3N2M1. The patient received therapy that included a XELOX regimen and trastuzumab. The XELOX regimen comprised 130 mg/m²

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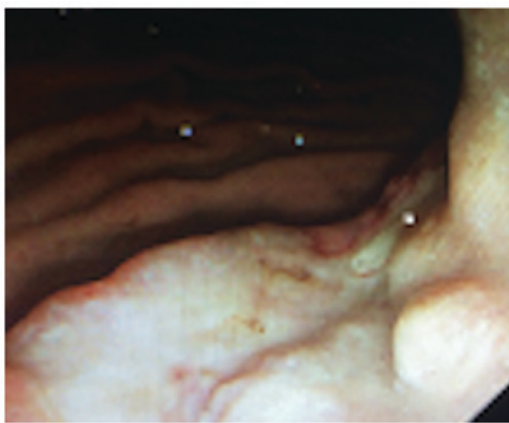


Figure 1. Gastroscopy prior to four cycles of trastuzumab combined with oxaliplatin and capecitabine.

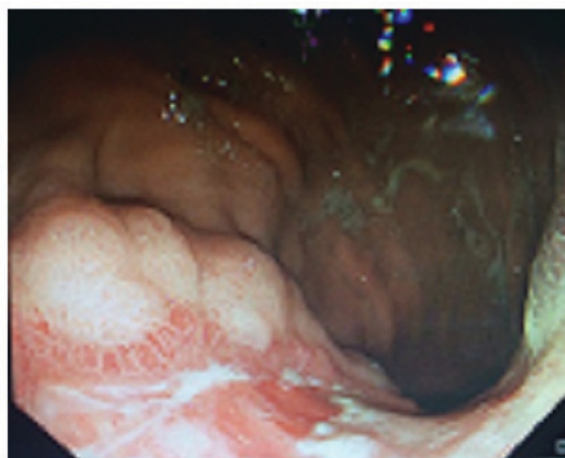


Figure 4. Gastroscopy following four cycles of trastuzumab combined with oxaliplatin and capecitabine.

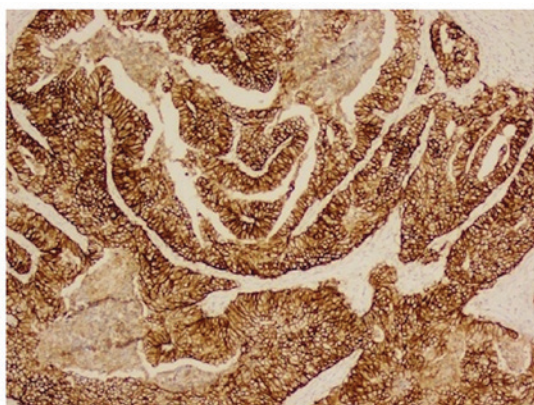


Figure 2. Immunohistochemical analysis revealed erb-b2 receptor tyrosine kinase 2 overexpression (3+). Magnification, x100.

oxaliplatin intravenous injection (iv) on day 1 and 1,250 mg/m² Xeloda[®] orally twice a day (p.o. b.i.d.) on days 1-14, repeated every 3 weeks. Trastuzumab was administered at 8 mg/kg iv on day 1 of the first cycle and then 6 mg/kg iv on day 1 of future cycles. Grade 1 neutropenia and grade 3 vomiting were observed based on the Common Terminology Criteria for Adverse Events (17). A CT scan was performed once the patient finished four cycles of the combination therapy. Partial response was observed using gastroscopy and CT (Figs. 4 and 5), and the clinical stage following four cycles of trastuzumab combined

with chemotherapy was cT2N1M0 (18). Subsequently, the patient underwent total gastrectomy, D2 lymphadenectomy and Roux-en-Y anastomosis. Exploratory surgery revealed a 10x8 cm size tumor in the gastric body with multiple regional lymph nodes enlarged. However, no metastatic nodules were identified in the liver, parietal peritoneum, mesentery, or pelvic floor. The macroscopic type of the tumor was classified as either the ulcerative or the infiltrative type according to Borrmann classification (19). Erosion mucosa, a small ulcer, and a rigid wall were detected. The pathological diagnosis was poorly differentiated adenocarcinoma of the gastric body. The tumor had invaded through the submucosa. Incisional margins were negative. In addition, cancer cells were identified in a lesser curvature lymph node (1/7 lymph nodes), whereas no cancer cells were observed in the other lymph nodes (0/16) (18). The pathological tumor-node-metastasis (TNM) stage was ypT1N1M0 (18). After six weeks following surgery, the patient received four cycles of XELOX and the trastuzumab regimen at the dose administered prior to surgery. After the therapy ceased, the patient received a follow-up every 3 months and remained disease-free at 12 months.

Case 2. A 67-year-old male was admitted to Sichuan Cancer Hospital with a complaint of abdominal pain for >3 weeks. Gastroscopy revealed an ulcer of the gastric cardia (Fig. 6) in July 2013. Biopsy identified a poorly differentiated carcinoma.

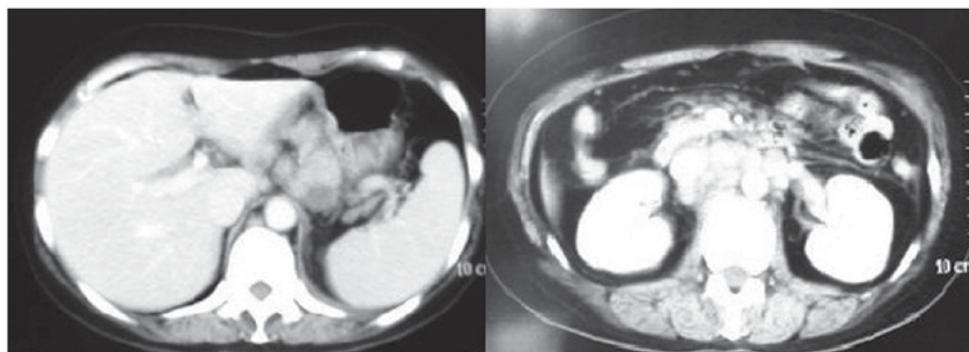


Figure 3. Computed tomography scan prior to four cycles of trastuzumab combined with oxaliplatin and capecitabine.

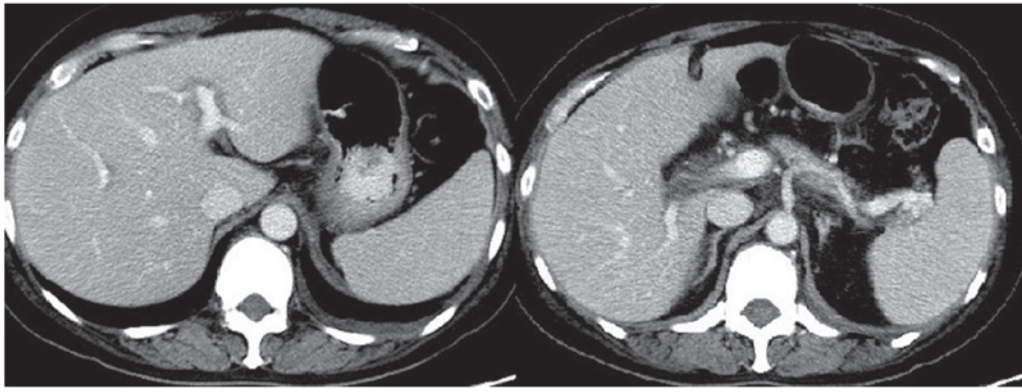


Figure 5. Computed tomography scan following four cycles of trastuzumab combined with oxaliplatin and capecitabine.



Figure 6. Gastroscopy prior to four cycles of trastuzumab combined with oxaliplatin and capecitabine.

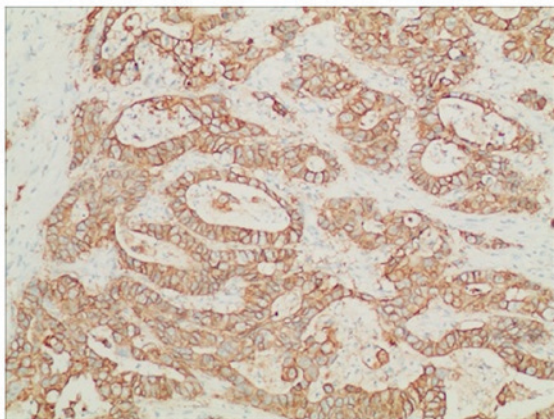


Figure 7. Immunohistochemical analysis revealed erb-b2 receptor tyrosine kinase 2 overexpression (3+) Magnification, x100.

Immunohistochemical analysis revealed ERBB2 overexpression (Fig. 7) (16). CT demonstrated a thickening of the cardia wall and that multiple lymph nodes were enlarged in the region of the lesser curvature of the stomach (Fig. 8). The clinical diagnosis was cardia carcinoma with abdominal cavity lymph node metastasis. The clinical stage was cT4aN2M0. The patient received a neoadjuvant therapy that included a XELOX regimen and trastuzumab. The XELOX regimen comprised

130 mg/m² oxaliplatin iv on day 1 and 1,250 mg/m² Xeloda p.o. b.i.d. on days 1-14, repeated every 3 weeks. Trastuzumab was administered at a dose of 8 mg/kg iv on day 1 of the first cycle and then 6 mg/kg iv on day 1 of future cycles. Grade 2 neutropenia and grade 3 vomiting were observed. A CT scan was performed after the patient finished four cycles of the combination therapy. The lymph nodes along the lesser curvature and the tumor decreased in size following treatment (Figs. 9 and 10). The clinical stage after four cycles of trastuzumab combined with chemotherapy was cT2N2M0. The patient underwent total gastrectomy, D2 lymphadenectomy and Roux-en-Y anastomosis following the four cycles of the combination therapy. Surgical exploration identified a 7x5 cm tumor in the cardia and fundus of the stomach, with enlarged lymph nodes, and no evident metastatic nodules in the liver, parietal peritoneum, mesenterium or pelvic floor. The macroscopic type of the tumor was classified as Borrmann III (19). The pathological diagnosis was poorly differentiated adenocarcinoma of the stomach. The tumor had invaded the muscular layer. Incisional margins were negative. In addition, cancer cells were identified in the lesser curvature lymph node (2/9), whereas no cancer cells were identified in other lymph nodes (0/10). The pathological TNM stage was ypT2N1M0. The patient received an additional four cycles of XELOX and the trastuzumab regimen at a decreased dose with 100 mg/m² for oxaliplatin and 1,000 mg/m² for Xeloda. After the therapy ceased, the patient received a follow-up every 3 months and remained disease-free at 13 months.

Discussion

Gastric cancer is the fourth most common cancer worldwide in 2008 and the high incidences of gastric cancer are reported in China, Japan and South Korea (20). Gastric cancer is the third most prevalent cause of cancer-associated mortality in males and the second most prevalent in females in China in 2011 (1). Unlike in Japan, screening programs are not performed in China, and the majority of patients with gastric cancer present at initial diagnosis in a more advanced stage (1).

For late stage gastric cancer, surgical resection does not represent the optimal strategy; palliative gastrectomy, chemotherapy, radiotherapy, gastric stent and bypass are the current strategies for these patients (4). The Japanese Gastric Cancer Association guidelines suggest that gastrectomy

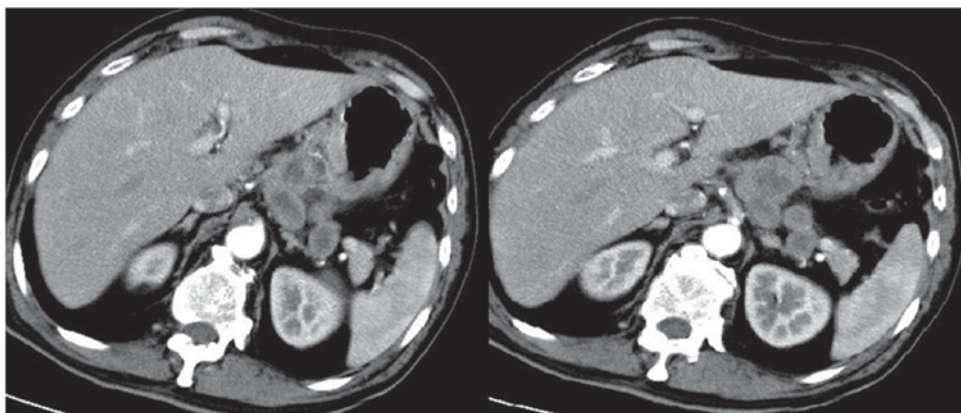


Figure 8. Computed tomography scan prior to four cycles of trastuzumab combined with oxaliplatin and capecitabine.

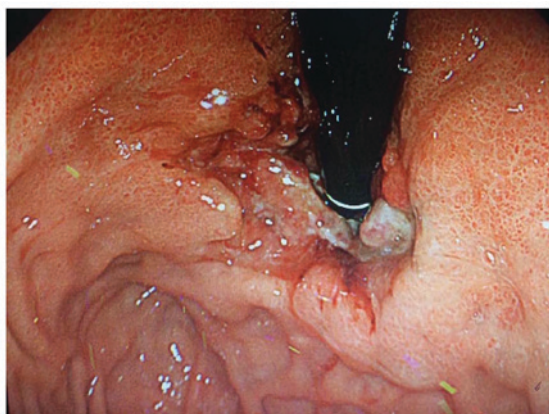


Figure 9. Gastroscopy following four cycles of trastuzumab combined with oxaliplatin and capecitabine.

ought to be performed for patients with a single non-curative factor (21). In contrast, the guidelines of three European societies, the European Society for Medical Oncology, the European Society of Surgical Oncology, and the European Society of Radiotherapy and Oncology, suggest that gastrectomy should be performed for patients who respond well to systemic chemotherapy (22). However, the REGATTA trial reported that palliative resection of the primary tumor was not beneficial for patients (23). Other previous studies have

demonstrated that palliative resection of the primary tumor following chemotherapy was beneficial for patients (24,25). Conversion surgery was defined as an initial tumor that was not suitable for surgery, therefore chemotherapy was administered to reduce the tumor size prior to surgical resection being performed (26). This conversion treatment may be the optimal choice for patients with late stage gastric cancer; chemotherapy compliance could be improved prior to surgery and certain cytokines may promote tumor growth following surgery (27,28).

In 1997, Nakajima *et al* first reported conversion surgery for gastric cancer (29). At the same time, they also reported that liver metastasis and peritoneal seeding were difficult to control (29). In addition, Kanda *et al* revealed that lymph node metastasis and peritoneal dissemination were associated with an improved, and poorer prognosis, respectively (30). To identify patients who may benefit from conversion therapy, Yoshida *et al* classified late stage gastric cancer into four categories; patients with potentially resectable metastases without peritoneal dissemination represented the optimal candidates for neoadjuvant chemotherapy, while those with marginally resectable metastases without peritoneal dissemination represented the optimal candidates for conversion surgery (31). In a recently reported clinical trial, 40/151 patients with gastric cancer underwent conversion surgery (32). The 5-year overall survival rate of the patients who underwent conversion surgery was 43%, whereas those

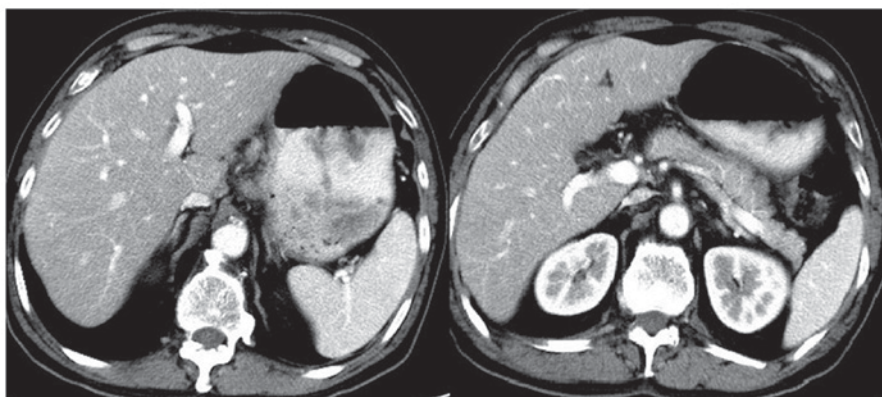


Figure 10. Computed tomography scan following four cycles of trastuzumab combined with oxaliplatin and capecitabine.

who were treated with chemotherapy alone were associated with an overall survival rate of 1%. The patients in the present study presented with lymph node metastasis and responded well to chemotherapy and targeted therapy. Therefore, conversion surgery was performed following four cycles of chemotherapy and targeted therapy.

The ToGA trial confirmed the efficacy and safety of trastuzumab (13). National Comprehensive Cancer Network guidelines suggest that all patients with metastatic disease should be tested for ERBB2 at the time of diagnosis (33). As a first-line treatment, the effectiveness of trastuzumab in palliative therapy has been supported by a previous study (13). Certain case reports have indicated that trastuzumab was successfully applied for conversion surgery in patients with gastric cancer (14,15). Similarly, ERBB2 (3+) was revealed in our patients assessed in the present study upon initial diagnosis of gastric cancer. In the patients evaluated in the present study, targeted therapy was combined with chemotherapy, the patients responded well, and conversion surgeries were performed in the patients. Conversion therapy is a novel therapy concept for which trials are expected.

The present study provided novel insight into conversion therapy for advanced stage gastric cancer. Further study is required to evaluate the efficacy of combining targeted therapy with a chemotherapy regimen in patients with gastric cancer.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

SX and XZ wrote the main manuscript. SX and XZ made contribution to conception and design. SX, RX and ZD performed the data collection. XT and JL prepared the figures and made contribution to the pathological data collection.

Ethics approval and consent to participate

Written informed consent was obtained from the patients for the present study and any accompanying images to be published. The Ethics Committee of Sichuan Cancer Hospital (Chengdu, China) approved the present study.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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