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Conversion Therapy for Advanced Gastric Cancer with Apatinib Combined with SOX Regimen: A Report of Two Cases and Literature Review

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Abstract

In late state gastric cancer, combination chemotherapy with targeted therapy has been employed, which may control the tumor growth and recurrence. We here report two patients diagnosed with advanced gastric cancer which were treated with SOX regimen combined with apatinib for conversion therapy. After three cycles of this combination treatment, the lymph node metastases and tumor decreased in size, which enabled the surgery (R0 resection), with no recurrence for more than 1 year. We believe that apatinib combined with SOX regimen can increase the possibility of successful surgical resection, and thereby prolonging the progression-free survival of patients with advanced gastric cancer.

Keywords: Gastric cancer • Conversion therapy • Tyrosine kinase inhibitor • Apatinib

Introduction

Gastric Cancer (GC) is a common digestive system neoplasm and the third leading cause of cancer related death worldwide [1-3]. The prognosis of Advanced Gastric Cancer (AGC) remains dismal in China because most of the cases were already in advanced or even late stage when admitted to hospital [4]. Comprehensive therapy based on chemotherapy is considered to be the optimal treatment for patients with AGC. Neo Adjuvant Chemotherapy (NAC) has been recommended for respectable, locally AGC in most international Western guidelines [5]. Conversion therapy, which defined as surgical treatment aimed at R0 resection post-chemotherapy for tumours that originally considered being unrespectable or marginally respectable for technical and/or oncological reasons recently have shown some good prospects and provided more opportunities in AGC patients [6-10]. Therefore, conversion therapy has attracted great attention as a new therapeutic Strategy for AGC patients. Apatinib [Aitan® (brand name in China)], a small molecule tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptor 2, which was invented in People's Republic of China and approved by the China Food and Drug Administration (CFDA) for further treatment in patients with AGC or esophagogastric junction adenocarcinoma [11]. There is limited evidence about the safety and feasibility of apatinib combined with SOX regimen as conversion therapy for AGC. In our recent work, two patients with AGC were treated with regimen consisted of aptinib, oxaliplatin and S-1 (SOX) was successfully performed following surgery with R0 resection. This attempt of combination strategy of conversion therapy was successful, and received good clinical outcomes.

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Case Series

Case 1

A 61-year-old male suffered from dysphagia for more than 1 month was admitted to AnHui Province Tumor Hospital in September 2018. No positive signs were found on physical examination. Serum CEA was 4.6 ng/ml (normal <6.5 ng/ml). Serum CA199 was 6.34 U/ml (normal <27.0 U/ml). Blood test showed no anemia (hemoglobin 145.00 g/L). Liver and renal function tests were normal. The patient had no special history of heart disease, diabetes, hypertension, and kidney-related diseases etc. Gastroscopy examination revealed a cardiac tumor, with a 3 cm ulcer in diameter and rough mucosa (Figure 1). Biopsy indicated a poorly differentiated adenocarcinoma. Computed Tomography (CT) scan revealed a thickening of cardiac, meanwhile multiple lymph nodes were found enlarged mainly around the lesser curvature of the stomach. The clinical stage of patient was defined as advanced gastric cancer (cT4N1M0). Considering the patient was without obvious bleeding and obstruction, conversion therapy was recommended for the optimal treatment. After signing informed consent, based on the patient's economic condition and willingness, the patient received the therapy which included a SOX regimen and apatinib (Hengrui Pharmaceutical Co., Ltd, Jiangsu, and China). The SOX regimen consisted 130 mg/m^2 oxaliplatin intravenous injection (iv) on day 1 and S-1 40 mg bid on day 1 to day 14, repeated every 3 weeks. Apatinib was administered daily 500 mg. Grade 1 neutropenia and grade 2 vomiting were observed based on the Common Terminology Criteria for Adverse Events (AEs) [12].

After three cycles of conversion therapy the patient received a CT scan which showed an apparent partial response, both the lymph nodes and tumor decreased in size (Figures 2-5). The clinical stage was redefined as cT2N0-1M0. Subsequently, the operation (total gastrectomy, D2 lymphadenectomy plus Roux-en-Y anastomosis) was performed 4 weeks later. Abdominal cavity exploratory surgery found a 2 × 1 cm size tumor in the gastric cardiac with multiple enlarged regional lymph nodes around the lesser curvature of the stomach. However, no obvious metastatic nodules were identified in the liver, mesenterium, parietal peritoneum, or pelvic floor. The postoperative pathological revealed that the tumor had invaded through the muscular is. A small ulcer with erosion mucosa and a rigid wall were detected at cardiac. The incisional margins were negative. In addition, three positive lymph node were identified in the lesser curvature (3/16 lymph nodes), whereas no positive lymph node were observed in the greater curvature of stomach (0/7). The pathological Tumor Node Metastasis (TNM) stage postoperative was

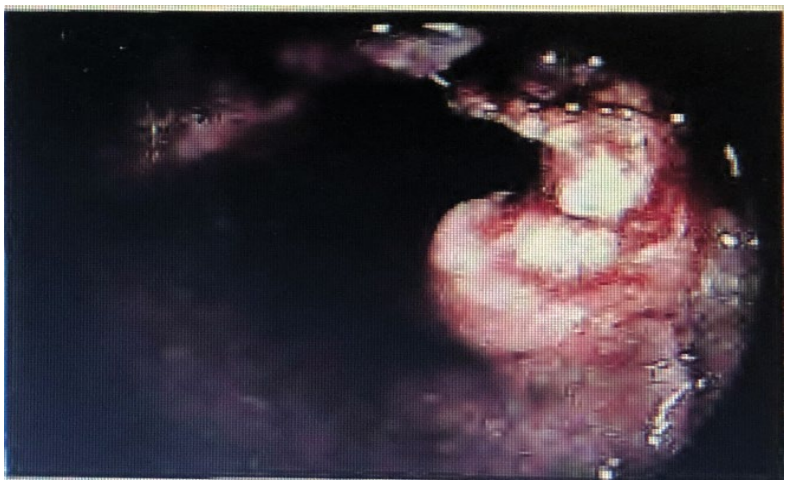
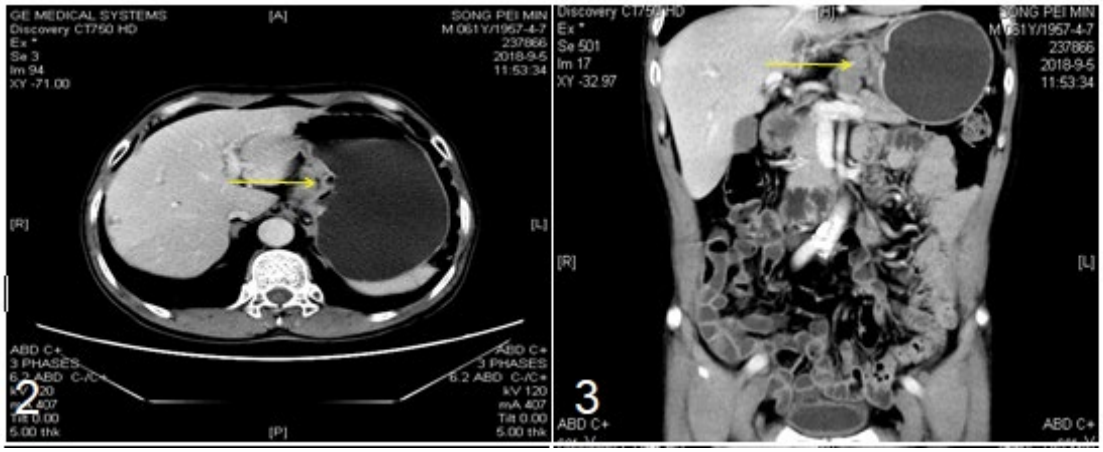
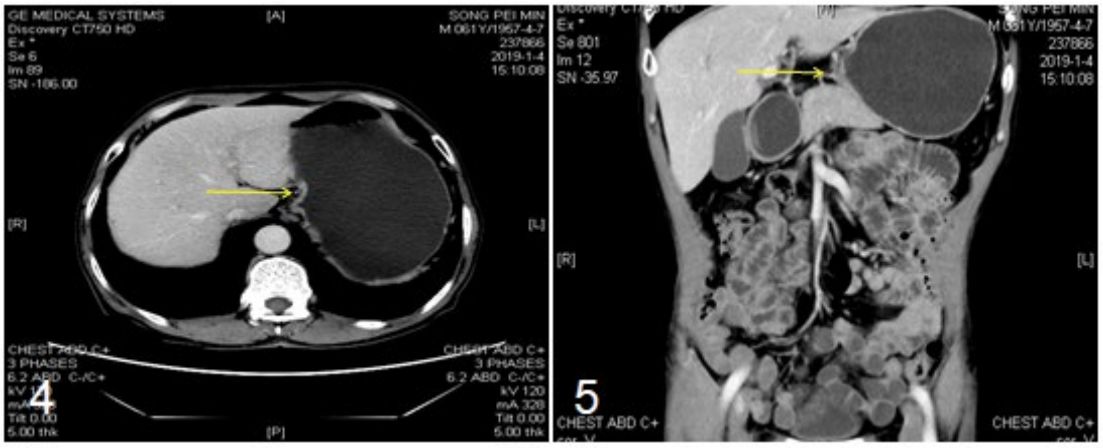


Figure 1. Gastroscopy revealed a cardiac tumor with a 3 cm ulcer in diameter and rough mucosa.



Figures 2 and 3. CT scan prior to conversion therapy.



Figures 4 and 5. CT scan following conversion therapy.

ypT2N1M0. After 1 month following surgery, the patient received further three cycles of SOX regimen and apatinib which at the dose administered before surgery. After all the therapy ceased, the patient received a follow-up every 3 months, and no recurrence was observed for more than 1 year after the surgery.

Case 2

A 52-year-old male suffered with increased bowel movements with anemia for almost 4 months was admitted to AnHui Province Tumor Hospital. No positive signs were found on physical examination. Blood test showed Moderate anemia (haemoglobin 73.00 g/L). Liver and renal function tests were normal. Serum CEA was 2.03 ng/ml (normal <6.5 ng/ml). Serum CA199 was 18.05 U/ml (normal <27.0 U/ml). The patient had a history of Hepatitis B. Gastroscopy examination showed irregular haemorrhagic ulcerative lesions extending from the gastric body to the lesser curvature of the stomach (Figure 6). Biopsy identified a poorly differentiated carcinoma. CT scan revealed a thickening wall of the cardiac and body with multiple lymph nodes were found enlarged around the lesser curvature of the stomach. Considering the diagnosis of gastric body carcinoma with abdominal cavity lymph node metastasis, the clinical stage was defined as advanced gastric cancer (cT3N2M0). Hence, the patient received a conversion therapy that included a SOX regimen and apatinib. The SOX regimen comprised 130 mg/m^2 oxaliplatin intravenous injection (iv) on day 1 and S-1 40 mg bid on day 1 to day 14, repeated every 3 weeks. Apatinib was

administered daily 500mg. Grade 1 neutropenia and grade 1 vomiting adverse reaction was observed.

Once the patient finished three cycles of the combined therapy, a CT scan was performed, which showed that the lymph nodes and the tumor decreased in size (Figures 7-10). Considering an apparent partial response of patient been achieved, the clinical stage was redefined as cT2-3N1M0. Hence, the patient underwent total gastrostomy, D2 lymphadenectomy plus Roux-en-Y anastomosis. Abdominal cavity surgical exploration identified a 4 × 3 cm tumor in the region of body and cardiac of the stomach. Some enlarged lymph nodes were found around the stomach, but no obvious metastatic nodules were found in the liver, mesenterium, parietal peritoneum, or pelvic floor. The postoperative pathological revealed that the tumor had invaded the sub mucosa, and incisional margins were negative. In addition, no positive lymph node was found both in the lesser curvature (0/23 lymph nodes) and greater curvature of stomach (0/20 lymph nodes). The TNM stage postoperative was ypT1bN0M0. After 1 month following surgery, the patient received further three cycles of SOX regime and apatinib at the dose prior to surgery. After the therapy ceased, the patient received a follow-up every 3 months and no recurrence was observed for more than 1 year after the surgery.

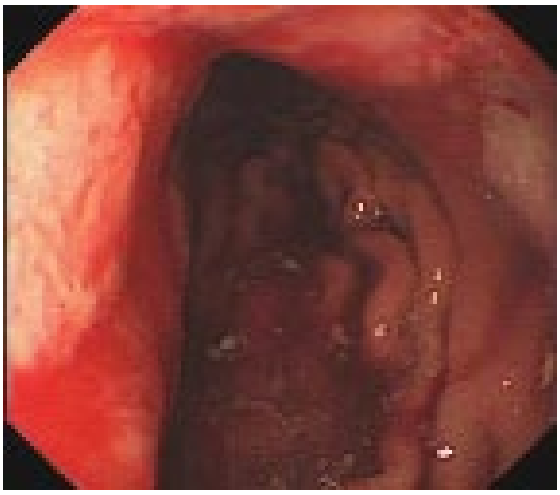
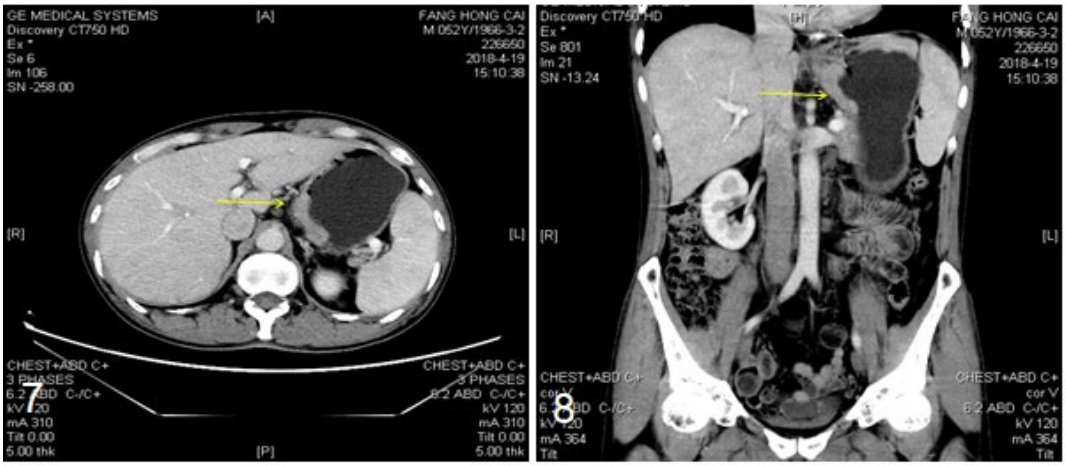
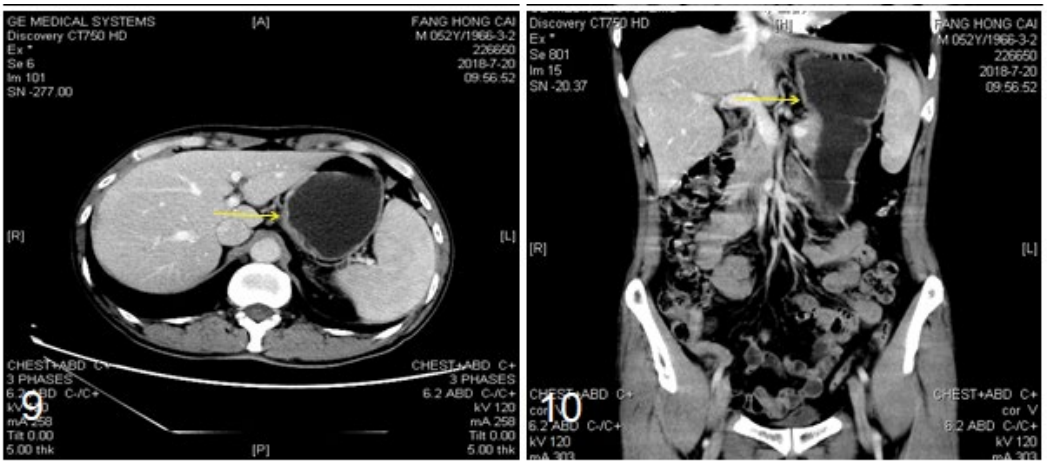


Figure 6. Gastroscopy revealed irregular hemorrhagic ulcerative lesions extending from the gastric body to the lesser curvature of the stomach.



Figures 7 and 8. CT scan prior to conversion therapy.



Figures 9 and 10. CT scan following conversion therapy.

Discussion

Tumor angiogenesis plays a vital role in the processes of tumor proliferation, migration, and metastasis, acting as nutrient supply for cancer cells. Therefore, antiangiogenic therapy has become a promising approach for the treatment of cancers [13,14]. The specific binding of Vascular Endothelial Growth Factor (VEGF) to Vascular Endothelial Growth Factor Receptor (VEGFR) can promotes the proliferation and migration of vascular endothelial cells, which progressively induces angiogenesis, increases vascular permeability, and additionally drives the proliferation, infiltration, and metastasis of tumor cell [15]. Targeting VEGF could be a promising therapeutic strategy for AGC since high levef of VEGF expression is one of the characteristic features of GC. Apatinib can decrease VEGF-mediated endothelial cell migration, proliferation, and density of the tumor microvasculature through selectively binds to and strongly inhibits VEGFR-2 [16,17]. The RAINBOW study found that the overall survival of patients was significantly prolonged via the addition of ramucirumab to Paclitaxel (PTX) chemotherapy alone [18]. Considering apatinib and ramucirumab share the same target, the combination of apatinib and SOX chemotherapy can be an attractive strategy for better clinical benefit. Over the last decade, many studies have found that the combination of targeted therapy with chemotherapy has better therapeutic benefit than the treatment of chemotherapy alone [19]. In the present work, we used apatinib combined with chemotherapy based on its efficacy in antiangiogenesis. The patients responded well to the combination therapy, and conversion surgery was successfully performed. Though the most common AEs of apatinib are hypertension, hand-foot skin reaction, and proteinuria, these are controllable and tolerable. Both the two cases of our study did not present obvious side effects but Grade 2 fatigue which was well managed.

Conclusion

In conclusion, our recent work provided novel insight into conversion therapy of AGC and showed that the therapy efficacy of conversion surgery may dramatically improve when combined with targeted therapy rather than chemotherapy alone. The response to apatinib from our patients showed that apatinib yield better survival rates of patients with AGC but also with a good safety and tolerability profile.

Ethics Approval and Consent to Participate

The Ethics Committee of west district of the first affiliated hospital (Anhui Province Tumor Hospital) of university of science and technology of China. (Hefei, China) approved the present study.

Patient Consent for Publication

Written informed consent was acquired from the patients for the present study.

Availability of Data Materials

The datasets used in the current study are available from the corresponding author.

Competing Interests

All the authors declare that have no competing interests.

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Author Contributions

ZhangJun, DaiYan, and Zhongliang Ning conceived the issues which formed the content of the manuscript and wrote the manuscript. All authors read and approved the final manuscript.

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