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Tumor recurrence after pathologic complete response in locally advanced gastric cancer after neoadjuvant therapy: two cases report

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Abstract

BACKGROUND

The pathologic complete response rate following neoadjuvant chemotherapy for advanced gastric cancer remains low and lacks a universally accepted treatment protocol. Immunotherapy has achieved breakthrough progress.

CASE SUMMARY

We report two female patients with gastric cancer defined as clinical stage (CT4N1-2M0), the detection of mismatch repair protein showed: mismatch repair function defect; programmed death protein 1 (PD-1) inhibitor combined with SOX (S-1+ oxaliplatin) in perioperative treatment obtained pathological complete response (pCR). Surprisingly, two patients underwent clinical observation after surgery but developed different degrees of metastasis at about six months after surgery.

CONCLUSION

PD-1 inhibitor combined with chemotherapy provides a more strategic choice for comprehensive perioperative treatment of gastric cancer. It is controversial for PCR patients to continue comprehensive chemotherapy or clinical observation after surgery.

INTRODUCTION

We report two female patients with gastric cancer defined as clinical stage (CT4N1-2M0). The detection of mismatch repair protein showed: mismatch repair function defect (dMMR); programmed death protein 1 (PD-1) inhibitor combined with SOX (S-1+ oxaliplatin) in perioperative treatment obtained pathological complete response (pCR). It is controversial for PCR patients to continue comprehensive chemotherapy or clinical observation after surgery. Surprisingly, two patients underwent clinical observation after surgery but developed different degrees of metastasis at about six months after surgery. This unexpected outcome prompted a review of the comprehensive perioperative treatment for these two patients in an effort to provide valuable insights for clinical decision-making.

CASE PRESENTATION

Chief complaints

The patient was an 81-year-old woman with upper abdominal pain, loss of appetite, belching, and acid reflux for 3 mo.

History of present illness

The patient complained of upper abdominal pain without obvious inducement 3 mo ago, accompanied by loss of appetite, belching, and gastric acid reflux. Before 1 mo, the above symptoms were aggravated, and eating difficulties and nausea occurred. Since the onset of the disease, her weight has dropped by 2 kg.

History of past illness

The patient had a history of hypertension and type 2 diabetes, and the oral medication was well-controlled.

Personal and family history

The patient had no relevant personal or family history.

Physical examination

Blood pressure of 130/82 mmHg (normal range: 90-140/60-90 mmHg), pulse rate of 72/min (normal range: 60-90/min), and respiratory rate of 18/min (normal range: 16-20/min).

Laboratory examinations

Blood tests revealed abnormal results: Carbohydrate antigen 19-9 count of 378.00u/mL (0-39.00u/mL); Carbohydrate antigen 72-4 count of 220u/mL (0-8.20u/mL); Carcinoembryonic antigen count of 478.00ng/mL (0-5.00ng/mL); hemoglobin count of 111 g/L (115 - 150 g/L).

Imaging examinations

CT was performed on the abdomen, showing gastric wall thickening in the lesser curvature of the antrum, gastric cavity stenosis with increased density of perigastric fat space, and multiple enlarged lymph nodes (**Fig1A, B, C**); Gastroscopy showed an ulcerative mass in the antrum, and pathology showed adenocarcinoma (**Fig1D and Fig2A**); Detection of mismatch repair (MMR) protein showed dMMR (**Fig3A, B, C, D**).

FINAL DIAGNOSIS

According to the Eighth American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) classification of neoplasm Metastasis (TNM) staging, gastric adenocarcinoma is defined as cT4N2M0 (clinical stage).

TREATMENT

This patient could benefit from immunosuppressive therapy.

From March 2021 to May 2021, the patients without chemotherapy contraindication received three cycles of SOX chemotherapy (intravenous oxaliplatin 130 mg/m^2 on day 1, S-1 80 mg/m^2 after breakfast and dinner twice daily on days 1 to 14), plus the PD-1 inhibitor (Camrelizumab) 200 mg ivgtt on day 1, q3w. Every three weeks was a cycle.

The treatment was well tolerated, and no immune-related adverse effects were observed based on tests for hematotoxicity and multiorgan function.

After three cycles of treatment, an abdominal CT scan performed on June 2, 2021, showed a significant reduction of antral mass and perigastric lymph nodes. The efficacy of therapy is defined as the partial response (PR) (**Fig 1E, F, G, H**). Laparoscopic comprehensive exploration and peritoneal lavage showed no metastasis and negative tumor cytology. Finally, gastric cancer D2 surgery was performed (June 2021), and the patient recovered and discharged smoothly.

OUTCOME AND FOLLOW-UP

After the D2 operation for Gastric cancer, postoperative pathological examination showed the pathological stage and ypCR of ypT0N0M0 (**Fig2B**).

Regular follow-up was required after postoperative communication with the patient. In December 2021, a liver ultrasound examination showed that two lesions in the right anterior lobe of the liver were considered metastatic, with liver biopsy indicating adenocarcinoma (**Fig2C**). Radiofrequency therapy for liver tumors was performed on January 5, 2022. Because the patient refused chemotherapy after the operation, she was followed up regularly and died on May 2, 2022. The entire diagnosis and treatment schedule of the patient is shown in **Fig 4**.

CASE 2

CHIEF COMPLAINTS

A 69-year-old female patient presented with cryptic pain in the upper abdomen and loss of appetite for 5 mo.

HISTORY OF PRESENT ILLNESS

The patient had upper abdominal pain for more than 5 mo, and vomiting occurred intermittently after eating. Since the onset of the disease, she body weight had decreased by 4.5 kg.

HISTORY OF PAST ILLNESS

Previous cholecystectomy due to gallstones.

PERSONAL AND FAMILY HISTORY

Drinking history of 40 years, no family history.

PHYSICAL EXAMINATION

Blood pressure of 120/70 mmHg (normal range: 90-140/60-90 mmHg), pulse rate of 62/min (normal range: 60-90/min), and respiratory rate of 17/min (normal range: 16-20/min).

LABORATORY EXAMINATIONS

Blood tests revealed abnormal results: CA19-9 count of 285.00u/mL (0-39.00u/mL); Carbohydrate antigen 72-4 count of 61.5u/mL (0-8.20u/mL); Carcinoembryonic antigen count of 5.48ng/mL (0-5.00ng/mL); hemoglobin count of 80 g/L (115 - 150 g/L).

IMAGING EXAMINATIONS

Gastroscopy showed masses in the antrum and gastric horn, and pathology showed heterospecific cells and signet-ring cells, CT of the abdomen showed local irregular thickening of the gastric wall in the antrum and gastric horn with clumped soft tissue shadows and enlargement of multiple lymph nodes around the stomach (**Fig5 A, B, C, D and Fig6 A**). Mismatch repair protein detection showed dMMR (**Fig7A, B, C, D**)

FINAL DIAGNOSIS

Gastric adenocarcinoma is defined as cT4N1M0 (clinical stage).

TREATMENT

This patient could benefit from immunosuppressive therapy.

From March 2021 to April 2021, two cycles of SOX chemotherapy regimen were administered in addition to the PD-1 inhibitor (Camrelizumab) (200 mg ivgtt on day1, q3w). The treatment was well tolerated, and no immune-related adverse effects were observed based on tests for hematotoxicity and multiorgan function.

After two cycles of treatment, the patient underwent an abdominal CT scan on April 14, 2021, which showed a decrease in antral mass and lymph nodes around the stomach. The efficacy of treatment is defined as PR (**Fig5E, F, G, H**). Laparoscopic comprehensive exploration and peritoneal lavage showed no metastasis and negative tumor cytology.Finally, gastric cancer D2 surgery was performed (May 2021), and the patient recovered and discharged smoothly.

OUTCOME AND FOLLOW-UP

After the D2 operation for Gastric cancer, postoperative pathological examination showed the pathological stage and ypCR of ypT0N0M0 (**Fig6B**).

Because the patient insisted on continuing postoperative treatment and could not tolerate therapy after one cycle with a Camrelizumab 200 mg ivgtt, she requested regular follow-up. In December 2021, the patient was given ascites due to apparent abdominal distension. Tumor cell examination showed dispersed nuclear heterogeneous cells in the ascites (Fig 6C). The patient was treated with a combination of PD-1 inhibitor and S-1 for two cycles because of intraperitoneal metastasis. Because gastrointestinal reaction occurred again, the patient failed tolerate the treatment and was given regular follow-up observations as well as nutritional support. The last follow-up time was October 2022. The entire diagnosis and treatment schedule of the patient is shown in **Fig 8**.

DISCUSSION

Gastric cancer constitutes a significant global health challenge, representing a leading cause of morbidity and mortality in the realm of gastrointestinal malignancies. As such, the standard treatment strategy for patients with a clinical assessment of ≥T3,

or advanced gastric cancer accompanied by lymph node metastasis, entails neoadjuvant therapy, surgery, and postoperative adjuvant therapy. However, the pathologic complete response (ypCR) rate following neoadjuvant chemotherapy for advanced gastric cancer remains low and lacks a universally accepted treatment protocol[1]. Increasingly, therapeutic combinations involving checkpoint inhibitors and other antitumor agents are being proposed for various types of cancers [2-4]. Of note, recent research within the field of gastric cancer has demonstrated a growing focus on immunotherapy, with several studies underscoring the efficacy of immune checkpoint inhibitors targeting the PD-1/ programmed death-ligand 1(PD-L1) in patients with advanced gastric cancer [5-8]. Consequently, combining a PD-1 inhibitor with chemotherapy has demonstrated considerable benefits in terms of overall survival (OS), progression-free survival (PFS), and tolerable safety profiles in comparison to chemotherapy alone [9]. Presently, Microsatellite Instability High (MSI-H)/dMMR is a recognized marker for forecasting the effectiveness of immunotherapy in gastric cancer [10]. Additionally, the NCCN clinical practice guidelines for gastric cancer advocate the use of PD-1 inhibitors for MSI-H/dMMR gastric cancer, which demonstrates progression post-chemotherapy [11]. Literature reveals a ypCR rate of 6% to 20% for neoadjuvant chemotherapy [12-14]. However, studies focusing on the ypCR status after neoadjuvant immunotherapy in gastric cancer are sparse. The ongoing GERCOR NEONIPIGA II study, however, is a promising development in this area and its forthcoming results are eagerly awaited [15]. Although there is little evidence for adjuvant chemotherapy in patients with ypCR after neoadjuvant therapy [16], a retrospective analysis involving 2676 patients with advanced gastric or gastroesophageal junction adenocarcinoma suggests that ypCR does not necessarily guarantee a cure. Surprisingly, ypCR patients had a high recurrence rate of 23%, including 36% developing brain metastases, compared to non-ypCR patients with a 4% incidence of brain metastases[17]. This raises questions about the effectiveness of adjuvant chemotherapy and whether there is undiscovered biological information

behind ypCR. Therefore, more studies are expected to compare the choices of treatment mode after ypCR.

CONCLUSION

There is a growing body of evidence suggesting that the augmented anti-tumor effect resulting from the synergistic action of chemotherapy and immunotherapy leads to a commendable remission rate and survival benefit. These positions the combinative approach as a promising trajectory in future oncologic treatments. Nevertheless, the rational and efficient amalgamation of chemotherapy and immunotherapy still presents a myriad of challenges, such as identifying the patient cohort that would optimally benefit from immunotherapy. Moreover, achieving a ypCR reflects a superb short-term treatment response, but it does not necessarily predict long-term survival. The potential for a less favorable prognosis underpins the necessity for rigorous postoperative surveillance and a collaborative effort across multiple disciplines, including medicine, surgery, radiotherapy, pathology, and translational medicine. It is anticipated that advancements in translational medicine can yield a more profound understanding of molecular biological information, as well as provide a more nuanced interpretation of tumor behavior. This, in turn, could pave the way for tailored treatment strategies for such patients.

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