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Abstract

BACKGROUND
Currently, chemotherapy combined with immunotherapy is the established frontline standard treatment for advanced gastric cancer (GC). In addition, the combination of radiotherapy and immunotherapy is considered a promising treatment strategy.

CASE SUMMARY
In this report, we present a case of achieving nearly complete remission of highly advanced GC with comprehensive therapies. A 67-year-old male patient was referred to the hospital because he presented with dyspepsia and melena for several days. Based on fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), endoscopic examination and abdominal CT, he was diagnosed with GC with a massive lesion and two distant metastatic lesions. The patient received mFOLFOX6 regimen chemotherapy, nivolumab and a short course of hypofractionated radiotherapy (4 Gy × 6 fractions) targeting the primary lesion. After the completion of these therapies, the tumor and the metastatic lesions showed a partial response. After having this case discussed by a multidisciplinary team, the patient underwent surgery, including total gastrectomy and D2 lymph node dissection. Postoperative pathology showed that major pathological regression of the primary lesion was achieved. Chemoimmuno-
therapy started four weeks after surgery, and examination was performed every three months. Since surgery, the patient has been stable and healthy with no evidence of recurrence.

CONCLUSION
The combination of radiotherapy and immunotherapy for GC is worthy of further exploration.

Key Words: Gastric cancer; Oligometastasis; Immunotherapy; Hypofractionated radiotherapy; Gastrectomy; Case report

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Core Tip: This case report describes a patient with unresectable advanced gastric cancer who received comprehensive treatment including chemoimmunotherapy and hypofractionated radiotherapy that was applied to treat the primary lesion; satisfactory efficacy was achieved. The combination of radiotherapy and immunotherapy is worthy of further exploration, and the dose division of radiotherapy is an important factor. Hypofractionated radiotherapy, compared to conventional fractionated radiotherapy, may better coordinate with immunotherapy.

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INTRODUCTION
According to GLOBOCAN 2020, gastric cancer (GC) ranks fifth and fourth in terms of the estimated number of new cases and the number of deaths worldwide, respectively[1]. Of note, the majority of worldwide GC cases and deaths occur annually in China, accounting for 43.9% of the worldwide cases and 48.6% of the worldwide deaths[1]. The median overall survival of patients with advanced GC is only 1 year[1,2]. Such disappointing survival outcomes are mainly the result of the inherent biological aggressiveness of GC and the relatively poor response to currently available therapies.

Cancer immunotherapy has opened a new era of cancer treatment. In 2020, two clinical studies based on KEYNOTE-059 and ATTRACTION-02 established the status of pembrolizumab and nivolumab as third-line treatments for advanced GC[3,4]. While moving from being a third-line treatment to a first-line treatment, immunotherapy for GC has encountered many difficulties and failures. Currently, chemotherapy combined with immunotherapy is the established first-line standard treatment for advanced GC[5].

At present, the focus of tumor immunotherapy has shifted from single-drug therapy to combined immunotherapy, as the combination could potentially lead to increased therapeutic efficacy. Radiotherapy can destroy tumor cells, promote the release of tumor antigens, and promote the infiltration of immune cells, thus changing the tumor microenvironment[6]. Therefore, the combination of radiotherapy and immunotherapy is considered a promising treatment strategy[6].

This report presents the case of a patient who was initially diagnosed with unresectable advanced GC and successfully treated with comprehensive therapies including chemotherapy, immunotherapy, and hypofractionated radiotherapy (HFRT). The tumor showed significant regression, and surgery was performed. Eventually, the patient achieved major pathologic regression.

CASE PRESENTATION

Chief complaints
A 67-year-old male patient presenting with dyspepsia and melena for several days was admitted to the Fudan University Shanghai Cancer Center (FUSCC, Shanghai, China) on May 12, 2022.

History of present illness
The patient developed dizziness, poor appetite, epigastrium fullness and discomfort, occasional dull pain, defecation, and no relief after taking omeprazole capsules for five days. Then the patient went to hospital accordingly.
History of past illness
The patient had no significant history of past illness.

Personal and family history
The patient had a past history of smoking and alcohol consumption for more than 30 years and had already quit smoking for 2 years. The patient had no significant family history.

Physical examination
Physical examination showed a pale face, indicating anemia (hemoglobin, 97 g/L). An enlarged lymph node was palpated in the left supraclavicular area. No positive signs were observed in abdominal and digital rectal examinations.

Laboratory examinations
The serum levels of carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen (CA) 19-9, CA125, CA72-4, CA50, and CA242 were all in the normal ranges.

Imaging examinations
Enhanced computed tomography (CT) scan of the stomach showed thickening of the wall of the gastric body and the antrum with enhancement, and multiple enlarged lymph nodes were detected around the stomach, hepatogastric space, hilar region, and retroperitoneum (Figure 1A). Gastroscopy indicated Borrmann type 3 GC, and pathology examination of gastroscopic biopsy suggested poorly differentiated adenocarcinoma with a proportion of signet ring cell carcinoma and the mixed type according to Lauren’s classification. Immunohistochemistry of biopsy tissue showed proficient mismatch repair (pMMR), HER2 2+ and EBER negativity. Fluorescence in situ hybridization (FISH) showed no HER2 amplification. Next-generation sequencing showed that the tumor mutation burden (TMB) was 5.98 muts/MB. Whole-body fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) showed the following findings: (1) Diffuse thickening of the gastric wall in the antrum and body with FDG hypermetabolism; (2) perigastric mesenteric turbidity; (3) metastatic lymph nodes visible around the stomach, hepatogastric space, hilar region, retroperitoneum, and left supraclavicular area; (4) left acetabular metastasis; and (5) a small amount of pelvic effusion (Figure 2).

FINAL DIAGNOSIS
The patient was diagnosed with metastatic GC (cT4N3M1, stage IV) according to the 8th edition of the Union for International Cancer Control TNM classification for GC.

TREATMENT
First-line standard treatment was performed, including the mFOLFOX6 regimen and a programmed death-1 (PD-1) inhibitor. The mFOLFOX6 regimen was applied as follows: oxaliplatin (85 mg/m$^2$) was injected intravenously within 2 h on day 1; leucovorin (400 mg/m$^2$) was injected intravenously within 2 h on day 1; 5-fluorouracil (400 mg/m$^2$) was injected intravenously and then was continuously infused (2400 mg/m$^2$) within 46 h; chemotherapy was repeated every two weeks. Nivolumab 240 mg was administered every two weeks. Considering that the patient was bleeding from gastric lesions and that the distal gastric tumor induced incomplete obstruction, we decided, after detailed communication with the patient and his family, to add radiotherapy for the primary lesion. After two cycles of chemoimmunotherapy, HFRT targeted to the primary lesion and lymphatic drainage area was performed with a total dose of 24 Gy split into 6 fractions. Then, another four cycles of chemoimmunotherapy were performed.

OUTCOME AND FOLLOW-UP
One month after these treatments, whole-body FDG PET/CT and enhanced abdominal CT were performed to evaluate the treatment effect. The adverse events (AEs) of the treatment were assessed according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 4.0. AEs included grade 1 gastrointestinal discomfort and grade 2 leukocytopenia. These side effects were resolved after symptomatic treatment, and leukocytopenia was relieved by using granulocyte colony-stimulating factor (G-CSF). The patient’s dyspepsia and melena were relieved remarkably. His tumor markers were still in the normal ranges. Enhanced CT scan of the stomach showed a decrease in the thickness of the gastric wall and the size of the perigastric lymph nodes (Figure 1B). There was an obvious reduction of the gastric lesions and metastatic lymph nodes with a lowered FDG metabolism.
Figure 1 Enhanced computed tomography images prior to and after combined treatment. A: Enhanced computed tomography (CT) before any treatment showed a lesion in the gastric wall; B: Enhanced CT after combined treatment revealed that the lesion was apparently decreased in size.

The FDG metabolism of the left acetabular metastasis and left supraclavicular lymph nodes tended to be normal (Figure 2). The clinical response was classified as partial response according to the Response Evaluation Criteria in Solid Tumors version 1.1.

Afterward, the case was submitted for multidisciplinary team discussion of GC in FUSCC, and surgery was cautiously recommended. Surgery was performed on October 20, 2022. Laparoscopic exploration found neither ascites nor peritoneal seeding. Therefore, laparoscopic surgery was converted to an open approach, and total gastrectomy with Roux-en-Y reconstruction and D2 lymph node dissection was performed. The histological change was classified as TRG grade 1, according to the National Comprehensive Cancer Network clinical practice guidelines in oncology for GC. Postoperative pathology showed that the tumor bed had ulceration with interstitial fibrosis and inflammatory cell infiltration, which was consistent with the changes after treatment. Combined with the immunohistochemical results, a small number of epithelioid cells, AE1/AE3+, were found within the mucosa, tending to be poorly differentiated adenocarcinoma with changes after treatment. Twenty-six lymph nodes were harvested without tumor metastasis. Thus, the postoperative staging was ypT1aN0Mx. There were no postoperative complications observed. The postoperative treatment plan involved the continuous use of the original regimen and then maintenance with nivolumab until one year after surgery. Chemoimmunotherapy started four weeks after surgery and examinations were performed every three months.

DISCUSSION

This study describes a patient with oligometastatic GC who received comprehensive treatment, including chemotherapy, radiotherapy, immunotherapy, and surgery. Pronounced remission of the primary lesion was achieved, as shown by FDG PET/CT and validated by postoperative pathology. Meanwhile, the metabolism of bone metastasis and left supraclavicular lymph nodes was also significantly reduced. In contrast to standard treatment, along with chemotherapy and immunotherapy, the primary lesion was also treated with HFRT due to bleeding and incomplete obstruction.

There is a special group of patients with stage IV disease, termed oligometastatic disease, who are in a relatively early and stable state without the tendency of metastasis spreading throughout the body. The number and location of metastatic lesions are limited, and it is believed that long-term survival can be achieved through systemic treatment with local treatment[7,8]. In gastroesophageal (GEJ) tumors, surgery, as a local treatment, is included in systemic treatment and brings survival benefits to patients with oligometastasis, which has been confirmed in the AIO-FLOT3 study[9]. Moreover, a subsequent AIO-FLOT5 study is in progress[10].

With the wide application of immunotherapy, radiotherapy combined with immunotherapy is considered a promising strategy due to its effect on immune activation and tumor microenvironment remodeling. Besides, enhanced mitochondrial metabolism plays an important role in the better treatment response to anti-PD1 agents[11] and radiotherapy[12]. The combination of immunotherapy and radiotherapy can cure patients with oligometastatic tumors, which has been proven in non-small cell lung cancer[13,14], prostate cancer[15], and other tumors[16]. However, the options of radiotherapy, including the sequence, dose, fractionation, and irradiated sites, that exert the best synergies need to be explored and optimized.

The conventional radiotherapy fraction mode is routinely used in GC. Selected studies have attempted HFRT for palliative treatment, especially for curing hemostasis, and several retrospective studies have indicated its good efficacy and safety[17-21]. However, the application of HFRT in GC is
Figure 2 Fluorodeoxyglucose positron emission tomography/computed tomography images prior to and after combined treatment. A: Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) prior to any treatment showed a large gastric mass with hypermetabolism, and the lesion was clearly decreased in size and metabolism after combined treatment; B: FDG PET/CT prior to any treatment showed hypermetabolism in the left supravacular area, and the lesion was clearly decreased in size and metabolism after combined treatment; C: FDG PET/CT prior to any treatment showed hypermetabolism in the left acetabular area, and the lesion was clearly decreased in size and metabolism after combined treatment.

Li et al[22] reported a prospective phase I study (ClinicalTrials.gov identifier: NCT03427684) of HFRT for the neoadjuvant treatment of GC. This was a dose-escalating study that included three levels of radiotherapy doses: 40.0 Gy/2.5 Gy/16 fractions, 95% isodose line covering the planning target volume (PTV); 95% PTV 41.6 Gy/2.6 Gy/16 fractions; and 95% PTV 43.2 Gy/2.7 Gy/16 fractions. Ultimately, 40.0 Gy/2.5 Gy was determined to be the maximum tolerated dose. Another single-arm prospective study (ClinicalTrials.gov identifier: NCT04162665) from the University of Washington in the United States adopted a short course of HFRT, sequential consolidation chemotherapy, and surgery for locally advanced GC. HFRT adopted a 5 Gy × 5 model with magnetic resonance guidance. The primary endpoint of this study was the pathologic complete regression rate. A single-arm prospective Phase Ib study (ClinicalTrials.gov identifier: NCT04523818) from MD Anderson Cancer Center in the United States explored the efficacy of short-course radiotherapy, sequential consolidation chemotherapy, and surgery in patients with resectable GC. The short course of radiotherapy in this study was divided into 10 fractions and completed within 2 wk. The primary endpoint was the incidence of AEs.

In preclinical models, HFRT has been proven to have better immune activation and less impact on lymphocytes[23,24]. In clinical practice, it seems that HFRT may show advances in certain cancers, and the combination of cancer immunotherapy and HFRT may have more potential[25]. Moreover, HFRT has the advantage of shortening the total treatment duration and saving medical resources. All these findings indicate that HFRT is a direction worth exploring in GC not only in the palliative setting but also in perioperative or treatment for oligometastatic patients.

Based on the aforementioned background, a Phase II clinical trial is being carried out in our center. This study targets patients with gastric/GEJ adenocarcinoma with limited liver metastases or paraaortic lymph node metastases. On the basis of systemic chemotherapy and immunotherapy, combined with HFRT of primary and metastatic lesions, the patients whose lesions can be surgically resected after treatment will receive surgery for primary and metastatic lesions when possible. The primary end point of the study was overall survival.
CONCLUSION

This study describes a patient with unresectable advanced GC who received comprehensive treatment; satisfactory efficacy was achieved. HFRT was applied to treat the primary lesion. The combination of radiotherapy and immunotherapy is worthy of further exploration. At the same time, the dose division, radiation range, choice of chemotherapy drugs, and arrangement of treatment sequence of radiotherapy need to be explored to better coordinate with immunotherapy.

FOOTNOTES

Author contributions: Zhou ML and Xu RN collected the pathological, biological, and clinical data; Zhou ML drafted the initial manuscript; Tan C reviewed the pathological results; Wan JF and Zhang Z reviewed or revised the manuscript and approved the final version; Wan JF had full access to all data and had final responsibility for the decision to submit for publication; and all authors contributed to the article and approved the submitted version.

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