Successful conversion of advanced gastric cancer treated by immunotherapy combined with chemotherapy: A case report

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Author contributions
Li-Min Huang conceived and designed the study. Xue-Mei Sun, Fu-Rong Sun, and Hai Yu were responsible for data acquisition. Xue-Mei Sun conducted the analysis and interpretation of the data. Han-Yi Yao and Ming-Chen Liu performed the statistical analysis. Wei-Wei Zheng, Xue-Mei Sun, and Fu-Rong Sun revised the manuscript for important intellectual content. Xue-Mei Sun drafted the manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
CT, computed tomography; SD, stable disease; PR, partial remission; CR, complete response; pCR, partially complete recovery; CPS, combined positive score; CTC, circulating tumor cell; MRD, minimal residual disease; ctDNA, circulating tumor DNA; CSCO, Chinese Society of Clinical Oncology; TCM, Traditional Chinese medicine.

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Abstract
Gastric cancer is one of the most common malignant tumors, for patients with advanced gastric cancer, the traditional treatment is mainly chemotherapy or combined targeted therapy; however, these have not achieved ideal efficacy. However, with the continuous deepening of research on molecular targeted drugs and immunosuppressants, the treatment of advanced gastric cancer patients has made new progress, and some new technologies have also been continuously emerged and applied, which brings hope for the treatment of advanced gastric cancer. Recently, several multicenter randomized controlled phase III studies on immunotherapy for advanced gastric cancer yielded encouraging results, demonstrating its superior efficacy in the treatment of advanced gastric cancer. However, prospective data to support the acceptance of surgery and the R0 removal rate following conversion therapy with immune checkpoint inhibitors are lacking. In this study, a 58-year-old woman with advanced gastric cancer and positive PD-L1 expression, negative HER-2 expression, and microsatellite stable status received immunotherapy combined with traditional Chinese medicine to achieve R0 resection and satisfactory efficacy.

Keywords: late gastric cancer; conversion therapy; immunotherapy; Traditional Chinese medicine

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Background

Gastric cancer is third leading cause of cancer-related deaths worldwide [1]. Because early gastric cancer has no evident symptoms, and people lack sufficient attention, most patients are diagnosed at a late stage or have developed distant metastasis and have lost the opportunity for radical surgery [2]. Therefore, improving the prevention and treatment level of gastric cancer has become a serious problem in the medical field.

Medical history data

A 58-year-old female patient (The patient is informed about and consents to this study.) presented with abdominal distension, gastric retention, and pain on January 27, 2023. Her computed tomography (CT) findings revealed irregular thickening and strengthening of the gastric antrum and curving walls of the stomach. Considering the possibility of gastric calcium, thickening of the surrounding greater omentum, and multiple lymph node metastases, a gastroscopy was also performed. Calcification in the mediastinum was observed, and a slight low-density shadow was observed in the junction area of the left lobe of the liver, which was considered a pseudotumor. Her pelvic CT revealed no significant abnormalities. Gastroscopic pathology combined with routine pathology 202306347 (gastric antrum) with immunohistochemical results were consistent with poorly differentiated adenocarcinoma. Immunohistochemistry findings revealed the following: CD56 (−), CerBb-2 (0), CgA (−), CK (broad spectrum) (+), CK7 (+) Ki67 (approximately 40% positive), MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), Syn (−), and Villin (+). In situ hybridization results revealed Epstein-Barr virus (EBV) encoded small nuclear RNAs (EBER) (−). Three cycles of CAPEOX combined with immunotherapy (oxaliplatin 150 mg d1 + cisplatinum 200 mg d1 + capecitabine 1.5 g d1–14, Q21d) were administered on February 3, 2023, February 24, 2023, and March 19, 2023, during which the treatment was combined with traditional Chinese medicine syndrome differentiation based on the principle of strengthening and suppressing tumor. Adverse reactions, including digestive tract reaction grade I and drug-induced liver injury grade I, were observed. Preoperative pathology of the Weifang People’s Hospital pathology of S202307253E. The immunohistochemical results were as follows: MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), PD1 (lymphocyte positivity rate was approximately 5%) (Figure 1), and CerBb-2 (0). The in situ hybridization revealed EBER (−). On May 2, 2023, her positron emission tomography and computed tomography scan following treatment of gastric carcinoma demonstrated a thickened wall of the gastric angulus–antrum and slightly increased metabolism, which were considered preservation of tumor activity. No abnormal metabolite small lymph nodes in the hepatogastric space or perigastric space were observed. The patient was advised to visit the clinic and assess for abnormal liver metabolism, slightly low-density nodules, or hemangiomas. Considering the adenomas on the left renal line, fibrous foci in both the lungs and calcification in the mediastinum and both pulmonary hilum were noted. No significant abnormal metabolism was identified in the remaining PET/CT scans. On May 6, 2023, she was admitted to the Weifang People's Hospital to undergo radical gastrectomy under general anesthesia (D2B2 + Braun). Routine postoperative pathology revealed the following: in the resection specimen of gastric cancer after chemotherapy (distal stomach), only a few poorly differentiated adenocarcinomas were detected in the submucosa, most of which were mucinous adenocarcinomas, and a few were signet ring cell carcinomas. The microscopic area was approximately 0.5 cm × 0.3 cm, accompanied by peripheral fibrous tissue hyperplasia and partial inflammatory cell infiltration. No cancer embolus or nerve invasion was identified in the vasculature. The incision margins of the anal and feeding end, as well as the serosal surface, were clear. No metastases were observed in the lymph nodes (0/17 and 0/11 in the lesser and greater curvatures, respectively). No cancer metastasis was observed in omental tissue; acute and chronic inflammation of the gastric mucosa, accompanied with ulcer formation and local suppurative changes; Lauren’s classification; diffuse type; pathological stage: ypT1bN0Mx, tumor regression grade I were noted. Chemotherapy combined with immunization for two cycles (cisplatinum 200 mg d1 + capecitabine 1.5 g bid d1–14, Q21d) was provided on June 8, 2023 and July 5, 2023, and three cycles of CAPEOX combined with immunotherapy (oxaliplatin 130 mg d1 + cisplatinum 200 mg d1 + capecitabine 1.5 g d1–14, Q21d) was provided on July 29, 2023. On October 18, the last treatment of 3 cycles of Cisdilizumab combined with Tighio maintenance therapy will be on December 3, 2023. The side effects included grade II myelosuppression, digestive tract reaction I, and grade I drug-induced liver injury. On August 24, 2023, the efficacy of CT was evaluated as stable disease (SD). After three cycles of conversion therapy, the degree of gastric wall thickening in the patient was significantly reduced, and the tumor index CA19-9 decreased from 95.30 U/mL to 13.85 U/mL. The curative effect was evaluated as partial remission (PR). The simplified medical chart is shown in Figure 2.

Suitable population and operation time for conversion therapy of advanced gastric cancer

Conversion therapy refers to the treatment of patients with advanced tumors that cannot be resected or can barely be resected owing to technical surgical reasons or oncological factors by means of preoperative treatment [3]. Conversion therapy must first reasonably screen benefit groups of conversion therapy. Some scholars believe that the benefit groups of conversion therapy are patients with distant ‘oligogenic’ metastasis or limited distant metastasis. The new biological classification proposed by Yoshida et al, is currently the most widely accepted basis for surgical decision making [4]. He divided patients with stage IV disease into four categories: category 1, resectable metastasis, no peritoneal involvement but with liver or peritoneal metastasis, localized paraaortic lymph node metastasis (no.16a2/16b1) or free abdominal cancer cells; category 2, potential resectable metastasis, which refers to multiple liver metastases or metastases > 5 cm in diameter; tumor invasion of vena cava or portal vein, accompanied by distant lymph node metastasis, etc. Such patients should receive chemotherapy to reach PR or CR preoperatively; category 3, peritoneal metastases visible to the naked eye without metastases to other organs; and class 4, both peritoneal and other organ metastases are present. Based on this classification,

Figure 1 PD-L1 staining. The patient was PD-1 positive and the CPS score was 5, suggesting that the patient belonged to the population benefiting from immunotherapy.

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Yoshida proposed objective principles for conversion therapy and considered class 2, some class 3, and a minority class 4 as suitable populations for conversion therapy. One group was excluded in the conversion therapy group because it could undergo primary resection or metastatic resection before chemotherapy or after neoadjuvant therapy without conversion therapy.

However, the timing of surgery after conversion therapy remains controversial. In theory, as long as R0 resection can be performed, regardless of whether the conversion treatment effect is CR, PR, or SD, surgery can be performed. However, the relationship between the efficacy of conversion therapy preoperatively and survival rate after R0 resection remains unclear. NCT04267549 studied the use of sindilizumab [5] combined with chemotherapy and targeted drugs as conversion therapy in patients with advanced unresectable gastric cancer. Among the 55 patients, 33 underwent conversion surgery; the success rate of surgical conversion was 60%, the R0 resection rate was 66.7%, and the partially complete recovery (pCR) rate was 15.2%. The best time for surgery is when the patient demonstrates the best response to chemotherapy; however, this time is often difficult to determine in clinical practice. Currently, conversion therapy is commonly performed with four to eight cycles of drug therapy based on clinical experience, during which the efficacy of imaging is evaluated every two to three cycles.

However, most experts currently believe that comprehensive treatment, including drugs, should be administered for patients who are not suitable for conversion therapy (category 4 patients according to the Yoshida classification). The REGATTA study [7] has demonstrated that palliative resection combined with postoperative chemotherapy had no OS benefit compared to chemotherapy alone, and the incidence of adverse reactions was significantly higher than that in the chemotherapy group. Some scholars also believe that palliative surgery can appropriately prolong the survival period of patients because it can relieve symptoms and resolve acute complications such as obstruction, perforation, and bleeding. A recent retrospective cohort study and meta-analysis has reported [8] significantly longer PFS (12 months vs 9 months) in patients who underwent palliative resection combined with chemotherapy than in those who did not undergo resection combined with chemotherapy. However, the results of these two studies are diametrically opposed. Therefore, whether palliative surgery should be accepted is unclear, and an individualized treatment plan should be developed based on multidisciplinary comprehensive considerations.

The present case belonged to the third category of the Yoshida classification. After completing three cycles of conversion therapy, the patient demonstrated marked improvement. The Eastern Cooperative Oncology Group score changed from 2 to 1, the nutritional risk assessment score was 3, and nutritional support was provided. Figure 3 shows the changes of primary focus, hepatogastric lymph node metastasis, and greater omental metastasis before and after conversion therapy. After observing the therapeutic effect, the patient was eager to receive surgery; therefore, only three cycles of conversion therapy were performed. Fortunately, the operation was very successful and R0 resection was achieved. Figure 4 shows the pet-ct results of the patient after the operation, indicating that the wall of the gastric angular-antrum tube of the patient was thickened, and the metabolism was slightly increased. Considering that tumor activity remained, there were no abnormal metabolic small lymph nodes in the hepato-gastric space and perigastric space.

**Predictive biomarkers of immunotherapy for advanced gastric cancer**

Currently, immunotherapy for advanced gastric cancer is primarily based on PD-1 inhibitors, the main mechanism of which is to kill tumor cells by binding to the PD-1 receptor and blocking the binding of PD-1 and PD-L1. Therefore, PD-1/PD-L1 is currently the most commonly used biomarker for screening the benefits of immunotherapy. Several studies have demonstrated that patients with high PD-L1 expression benefit more from immunotherapy. In ORIENT-16 patients with a PD-L1 combined positive score (CPS) score of ≥ 5, the mOS in the Cindelizumab combined chemotherapy group was 5.5 months longer than that in the chemotherapy alone group (18.4 vs 12.9), whereas the mOS in the combined versus chemotherapy group was 15.2 vs 12.3 months in the whole population [9]. Therefore, the mOS of those with PD-L1 CPS score < 5 was at least 3.2 months less than those with CPS score ≥ 5. The study of Guo Honghai et al. has demonstrated that the pCR [10] rate of PD-1 CPS ≥ 5 and CPS < 5 patients was 66.7% vs 19.0% (P = 0.246). In addition, unpublished data from the ORIENT-16 trial indicated that patients with PD-1 CPS scores between 1 and 5 still exhibited some degree of benefit. Therefore, patients with high expression of PD-1/PD-L1 can benefit more from immunotherapy than patients with low expression, and the higher the expression level, the more obvious the benefit trend of OS, while the PD-L1 negative population is difficult to benefit.

However, in Keynote-059 [11], three patients with negative PD-L1 expression achieved CR (2.8%). In the Attract-2 trial, PD-L1 negative patients were also [12] observed to have a survival benefit. Thus, predictive biomarkers for gastric cancer immunotherapy are not limited to PD-1/PD-L1. Other predictive biomarkers include microsatellite instability, tumor mutational burden, and EBV. These biomarkers can be used to assess the benefits of immunotherapy from a pathological perspective. Tumor-infiltrating lymphocytes are currently the focus of research for predicting the efficacy of immunotherapy [13], and studies have demonstrated that a higher number of tumor-infiltrating lymphocytes may benefit from immune
Checkpoint inhibitors.

The patient was positive for PD-1 and had a CPS score of 5 (Figure 5), indicating that the patient belonged to the benefit group of immunotherapy. However, her HER-2 expression was negative. Therefore, a sindillizumab treatment regimen combined with CAPEOX was selected. As for prognosis, whether there were small residual tumor lesions, circulating tumor cell (CTC) detection was also selected for evaluation during postoperative adjuvant treatment.

Figure 3: The changes of primary focus, hepatogastric lymph node metastasis, and greater omental metastasis before and after conversion therapy. (A) Primary pre-treatment. (B) Primary post-treatment. (C) Interhepatogastric lymph node metastasis before treatment. (D) Interhepatogastric lymph node metastasis after treatment. (E) Greater omental metastases at pre-treatment. (F) Greater omental metastases at post-treatment.
Minimal residual disease (MRD) monitoring

MRD refers to very few tumor cells [14] that remain in the body during or after treatment, regardless whether the tumor cannot be detected on imaging or clinical examination. Several detection methods include polymerase chain reaction, next-generation sequencing, droplet digital polymerase chain reaction, and circulating tumor DNA (ctDNA) analysis.

Circulating tumor cells (CTCs) are tumor cells with the ability to invade lymphatic tissue and enter the blood circulation. It is closely related to the metastasis and deterioration of cancer and can be used for early tumor diagnosis, monitoring cancer recurrence and metastasis, predicting cancer prognosis, and guiding clinical treatment. cTcs and ctDNA are mainly used to identify patients with a high risk of recurrence after surgery, and continuous detection of ctDNA is helpful for the early detection of tumor recurrence [15]. The most common ctDNA mutations in gastric cancer are in TP53 (44%-55%), EGFR (20%), ERBB2 (20%), MET (15%), and APC (10%). Studies have demonstrated that patients with locally advanced gastric cancer with TP53 and MET amplifications have a poor prognosis [16]. Other gene mutation rates are closely related to disease progression, immunotherapy effects, and drug resistance.

The CTC value of the patient in this case was 2, indicating that the patient was at risk of recurrence. Thus, the CTC value should be continuously monitored, and the treatment plan should be adjusted timely. In October this year, the CTC value dropped to zero. The results suggest that the risk of recurrence is lower than before.

Postoperative assistance

The 5th edition of the Japanese Guidelines for the Treatment of Gastric Cancer pointed out that after lymph node dissection above D2, the postoperative pathology was stage II–IIIB, and adjuvant chemotherapy was required; however, no requirement [17] for stage I patients has been established. The indications for postoperative adjuvant chemotherapy in the CSCO guidelines for resectable gastric cancer are stages II and III advanced gastric cancer with a postoperative pathological stage after D2 radical resection and without preoperative treatment. Studies have revealed that the postoperative tumor recurrence risk of stage III gastric cancer is high, and the recurrence mode is mainly distant metastasis. Postoperative adjuvant chemotherapy can reduce the occurrence of recurrence and metastasis and improve the postoperative survival rate.

Currently, postoperative adjuvant regimens are mainly chemotherapeutic. SOX, XELOX, single-agent S-1, cisplatin plus capecitabine, and docetaxel S-1 are the most widely used regimens. Regarding postoperative adjuvant immunotherapy, the Attract-5 study selected patients with stage III gastric/gastroesophageal junction cancer who received adjuvant therapy after D2 or more extensive gastrectomies. The three-year OS of the nabolumab (PD-1 drug) + chemotherapy group was 81.5% vs 78.0% compared with that of the placebo + chemotherapy group. The patient did not meet the ultimate endpoint of RFS. High hope has been placed on immunotherapy as a postoperative adjuvant, but satisfactory results have not yet been achieved. In conclusion, the reason for its failure may be the relatively late stage of patients, mainly IIIC stage, and the proportion of PD-L1 positive population and TPS positive population is low, which affects the evaluation of immunotherapy efficacy. The JS001-045-III-GC study changed the program to PD-L1 positive patients. In studies related to perioperative treatment of gastric cancer, PD-L1 positive patients with relatively late stage and high risk of lymph node metastasis were selected, which is expected to improve the probability of success of the study. It is also hoped that an increasing amount of experimental evidence will support immunotherapy for postoperative adjuvant treatment of gastric cancer.

The patient with stage IV gastric cancer received seven cycles of immunotherapy combined with chemotherapy as postoperative treatment, spanning one year both pre- and post-operatively. Currently, the patient has completed adjuvant treatment at our hospital, with recent follow-up indicators within normal range. Regular visits will continue to monitor the patient’s prognosis.

TCM treatment

Traditional Chinese medicine believes that the main location of gastric cancer lies in the spleen and stomach, and the Qi (Qi is the origin of the universe and the most basic element that constitutes everything in the world. It is considered that qi is the most basic substance that constitutes the human body and also the most basic substance that maintains human life activities. Blood, a nutritious red liquid substance circulating in the veins, is one of the basic substances that constitute the human body and maintain human life activities.) deficiency of the spleen and stomach is the internal factor of the occurrence of this disease, and the external factor of the formation and development of gastric cancer is to feel the external evil poison.
Therefore, the treatment is mainly to support the healthy Qi, care for the spleen and stomach, supplemented by regulating Qi and activating blood, eliminating phlegm and removing dampness, clearing heat and detoxifying anti-cancer.

At present, traditional Chinese medicine is mainly auxiliary in the treatment of gastric cancer. Combined with modern medical treatment, it can improve the quality of life of gastric cancer patients, reduce the probability of metastasis and recurrence, and improve the survival rate. The combination of traditional medicine's holistic righting therapy with modern medicine's local chemoradiotherapy and targeted therapy has become a trend in the treatment of malignant tumors.

In this case, the patient presented with gastric cancer Qi and blood deficiency syndrome. The prescribed formula primarily aimed to tonify the spleen and Qi, comprising: Astragalus 12 g, Codonopsis 12 g, Dangcia 10 g, Cauleroba 12 g, Jujube 20 g, Magnolia officinalis 10 g, Perilla stem 9 g, Rhodiola rosea 6 g, Yam 10 g, and Wine Yellow Essence 6 g. This prescription was administered to the patient throughout the treatment, with one dose per day divided into two administrations. Modifications to the prescription were made according to changes in the patient's condition. In addition, the patient had drug-induced liver injury during treatment, and was given XiaoBupuleurum decoction to relieve liver and stomach. All in all, the clinical use of traditional Chinese medicine mainly plays a role in enhancing efficacy and reducing toxicity, and many adverse reactions caused by anti-tumor drugs cannot be treated by western medicine, or the therapeutic effect of Western medicine is not ideal. Therefore, many modern doctors are exploring the use of traditional Chinese and western medicine to treat gastric cancer. It is hoped that future researchers will standardize research methods and conduct clinical and experimental studies on the treatment of gastric cancer by integrated Chinese and Western medicine in an all-round, multi-angle, multi-level and multi-mechanism, so as to provide more targeted and safe treatment programs for patients.

Conclusions

Conversion therapy for advanced gastric cancer has shown progress, but challenges persist in areas such as treatment plans, patient selection, timing of surgery, and postoperative care. The patient is stable and receiving postoperative adjuvant therapy, with ongoing monitoring. Her nutrition and gastrointestinal function are improving. This case aims to assist clinicians, expand treatment approaches, and offer experimental data for clinical guidance.

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