

# World Journal of *Clinical Cases*

*World J Clin Cases* 2022 June 26; 10(18): 5934-6340



**MINIREVIEWS**

- 5934 Development of clustered regularly interspaced short palindromic repeats/CRISPR-associated technology for potential clinical applications  
*Huang YY, Zhang XY, Zhu P, Ji L*
- 5946 Strategies and challenges in treatment of varicose veins and venous insufficiency  
*Gao RD, Qian SY, Wang HH, Liu YS, Ren SY*
- 5957 Diabetes mellitus susceptibility with varied diseased phenotypes and its comparison with phenome interactome networks  
*Rout M, Kour B, Vuree S, Lulu SS, Medicherla KM, Suravajhala P*

**ORIGINAL ARTICLE****Clinical and Translational Research**

- 5965 Identification of potential key molecules and signaling pathways for psoriasis based on weighted gene co-expression network analysis  
*Shu X, Chen XX, Kang XD, Ran M, Wang YL, Zhao ZK, Li CX*
- 5984 Construction and validation of a novel prediction system for detection of overall survival in lung cancer patients  
*Zhong C, Liang Y, Wang Q, Tan HW, Liang Y*

**Case Control Study**

- 6001 Effectiveness and postoperative rehabilitation of one-stage combined anterior-posterior surgery for severe thoracolumbar fractures with spinal cord injury  
*Zhang B, Wang JC, Jiang YZ, Song QP, An Y*

**Retrospective Study**

- 6009 Prostate sclerosing adenopathy: A clinicopathological and immunohistochemical study of twelve patients  
*Feng RL, Tao YP, Tan ZY, Fu S, Wang HF*
- 6021 Value of magnetic resonance diffusion combined with perfusion imaging techniques for diagnosing potentially malignant breast lesions  
*Zhang H, Zhang XY, Wang Y*
- 6032 Scar-centered dilation in the treatment of large keloids  
*Wu M, Gu JY, Duan R, Wei BX, Xie F*
- 6039 Application of a novel computer-assisted surgery system in percutaneous nephrolithotomy: A controlled study  
*Qin F, Sun YF, Wang XN, Li B, Zhang ZL, Zhang MX, Xie F, Liu SH, Wang ZJ, Cao YC, Jiao W*

- 6050** Influences of etiology and endoscopic appearance on the long-term outcomes of gastric antral vascular ectasia

*Kwon HJ, Lee SH, Cho JH*

#### Randomized Controlled Trial

- 6060** Evaluation of the clinical efficacy and safety of TST33 mega hemorrhoidectomy for severe prolapsed hemorrhoids

*Tao L, Wei J, Ding XF, Ji LJ*

- 6069** Sequential chemotherapy and icotinib as first-line treatment for advanced epidermal growth factor receptor-mutated non-small cell lung cancer

*Sun SJ, Han JD, Liu W, Wu ZY, Zhao X, Yan X, Jiao SC, Fang J*

#### Randomized Clinical Trial

- 6082** Impact of preoperative carbohydrate loading on gastric volume in patients with type 2 diabetes

*Lin XQ, Chen YR, Chen X, Cai YP, Lin JX, Xu DM, Zheng XC*

#### META-ANALYSIS

- 6091** Efficacy and safety of adalimumab in comparison to infliximab for Crohn's disease: A systematic review and meta-analysis

*Yang HH, Huang Y, Zhou XC, Wang RN*

#### CASE REPORT

- 6105** Successful treatment of acute relapse of chronic eosinophilic pneumonia with benralizumab and without corticosteroids: A case report

*Izhakian S, Pertzov B, Rosengarten D, Kramer MR*

- 6110** Pembrolizumab-induced Stevens-Johnson syndrome in advanced squamous cell carcinoma of the lung: A case report and review of literature

*Wu JY, Kang K, Yi J, Yang B*

- 6119** Hepatic epithelioid hemangioendothelioma after thirteen years' follow-up: A case report and review of literature

*Mo WF, Tong YL*

- 6128** Effectiveness and safety of ultrasound-guided intramuscular lauromacrogol injection combined with hysteroscopy in cervical pregnancy treatment: A case report

*Ye JP, Gao Y, Lu LW, Ye YJ*

- 6136** Carcinoma located in a right-sided sigmoid colon: A case report

*Lyu LJ, Yao WW*

- 6141** Subcutaneous infection caused by *Mycobacterium abscessus* following cosmetic injections of botulinum toxin: A case report

*Deng L, Luo YZ, Liu F, Yu XH*

- 6148** Overlapping syndrome of recurrent anti-N-methyl-D-aspartate receptor encephalitis and anti-myelin oligodendrocyte glycoprotein demyelinating diseases: A case report  
*Yin XJ, Zhang LF, Bao LH, Feng ZC, Chen JH, Li BX, Zhang J*
- 6156** Liver transplantation for late-onset ornithine transcarbamylase deficiency: A case report  
*Fu XH, Hu YH, Liao JX, Chen L, Hu ZQ, Wen JL, Chen SL*
- 6163** Disseminated strongyloidiasis in a patient with rheumatoid arthritis: A case report  
*Zheng JH, Xue LY*
- 6168** CYP27A1 mutation in a case of cerebrotendinous xanthomatosis: A case report  
*Li ZR, Zhou YL, Jin Q, Xie YY, Meng HM*
- 6175** Postoperative multiple metastasis of clear cell sarcoma-like tumor of the gastrointestinal tract in adolescent: A case report  
*Huang WP, Li LM, Gao JB*
- 6184** Toripalimab combined with targeted therapy and chemotherapy achieves pathologic complete response in gastric carcinoma: A case report  
*Liu R, Wang X, Ji Z, Deng T, Li HL, Zhang YH, Yang YC, Ge SH, Zhang L, Bai M, Ning T, Ba Y*
- 6192** Presentation of Boerhaave's syndrome as an upper-esophageal perforation associated with a right-sided pleural effusion: A case report  
*Tan N, Luo YH, Li GC, Chen YL, Tan W, Xiang YH, Ge L, Yao D, Zhang MH*
- 6198** Camrelizumab-induced anaphylactic shock in an esophageal squamous cell carcinoma patient: A case report and review of literature  
*Liu K, Bao JF, Wang T, Yang H, Xu BP*
- 6205** Nontraumatic convexal subarachnoid hemorrhage: A case report  
*Chen HL, Li B, Chen C, Fan XX, Ma WB*
- 6211** Growth hormone ameliorates hepatopulmonary syndrome and nonalcoholic steatohepatitis secondary to hypopituitarism in a child: A case report  
*Zhang XY, Yuan K, Fang YL, Wang CL*
- 6218** Vancomycin dosing in an obese patient with acute renal failure: A case report and review of literature  
*Xu KY, Li D, Hu ZJ, Zhao CC, Bai J, Du WL*
- 6227** Insulinoma after sleeve gastrectomy: A case report  
*Lobaton-Ginsberg M, Sotelo-González P, Ramirez-Renteria C, Juárez-Aguilar FG, Ferreira-Hermosillo A*
- 6234** Primary intestinal lymphangiectasia presenting as limb convulsions: A case report  
*Cao Y, Feng XH, Ni HX*
- 6241** Esophagogastric junctional neuroendocrine tumor with adenocarcinoma: A case report  
*Kong ZZ, Zhang L*

- 6247** Foreign body granuloma in the tongue differentiated from tongue cancer: A case report  
*Jiang ZH, Xu R, Xia L*
- 6254** Modified endoscopic ultrasound-guided selective N-butyl-2-cyanoacrylate injections for gastric variceal hemorrhage in left-sided portal hypertension: A case report  
*Yang J, Zeng Y, Zhang JW*
- 6261** Management of type IIIb dens invaginatus using a combination of root canal treatment, intentional replantation, and surgical therapy: A case report  
*Zhang J, Li N, Li WL, Zheng XY, Li S*
- 6269** Clivus-involved immunoglobulin G4 related hypertrophic pachymeningitis mimicking meningioma: A case report  
*Yu Y, Lv L, Yin SL, Chen C, Jiang S, Zhou PZ*
- 6277** *De novo* brain arteriovenous malformation formation and development: A case report  
*Huang H, Wang X, Guo AN, Li W, Duan RH, Fang JH, Yin B, Li DD*
- 6283** Coinfection of *Streptococcus suis* and *Nocardia asiatica* in the human central nervous system: A case report  
*Chen YY, Xue XH*
- 6289** Dilated left ventricle with multiple outpouchings – a severe congenital ventricular diverticulum or left-dominant arrhythmogenic cardiomyopathy: A case report  
*Zhang X, Ye RY, Chen XP*
- 6298** Spontaneous healing of complicated crown-root fractures in children: Two case reports  
*Zhou ZL, Gao L, Sun SK, Li HS, Zhang CD, Kou WW, Xu Z, Wu LA*
- 6307** Thyroid follicular renal cell carcinoma excluding thyroid metastases: A case report  
*Wu SC, Li XY, Liao BJ, Xie K, Chen WM*
- 6314** Appendiceal bleeding: A case report  
*Zhou SY, Guo MD, Ye XH*
- 6319** Spontaneous healing after conservative treatment of isolated grade IV pancreatic duct disruption caused by trauma: A case report  
*Mei MZ, Ren YF, Mou YP, Wang YY, Jin WW, Lu C, Zhu QC*
- 6325** Pneumonia and seizures due to hypereosinophilic syndrome – organ damage and eosinophilia without synchronisation: A case report  
*Ishida T, Murayama T, Kobayashi S*
- 6333** Creutzfeldt-Jakob disease presenting with bilateral hearing loss: A case report  
*Na S, Lee SA, Lee JD, Lee ES, Lee TK*

**LETTER TO THE EDITOR**

- 6338** Stem cells as an option for the treatment of COVID-19  
*Cuevas-González MV, Cuevas-González JC*

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# Toripalimab combined with targeted therapy and chemotherapy achieves pathologic complete response in gastric carcinoma: A case report

Rui Liu, Xia Wang, Zhi Ji, Ting Deng, Hong-Li Li, Yan-Hui Zhang, Yu-Chong Yang, Shao-Hua Ge, Le Zhang, Ming Bai, Tao Ning, Yi Ba

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## Abstract

### BACKGROUND

Neoadjuvant or perioperative chemotherapy combined with surgery can reduce postoperative recurrence and improve the long-term survival rate of patients with locally advanced resectable gastric carcinoma. Nivolumab combined with chemotherapy has been recommended by the National Comprehensive Cancer Network guidelines as a first-line therapy for advanced gastric carcinoma/adenocarcinoma of the gastroesophageal junction and serves as the basis for immunotherapy combined with chemotherapy to become a neoadjuvant therapy. Herein, we report a case in which pathologic complete response was achieved by neoadjuvant administration of toripalimab, Herceptin, and docetaxel, oxaliplatin, calcium folinate, and fluorouracil (FLOT) chemotherapy followed by surgery for human epidermal growth factor receptor 2 (HER2)- and programmed death-ligand 1 (PD-L1)-positive locally advanced gastric carcinoma. We hope that this case will shed some light on neoadjuvant therapy for gastric carcinoma.

### CASE SUMMARY

The patient was diagnosed with locally advanced adenocarcinoma of the cardia. Immunohistochemistry of the baseline tissues suggested that the tissues were HER2- (fluorescent *in situ* hybridization) and PD-L1-positive (combined positive score = 1). The patient underwent surgery following a four-cycle neoadjuvant therapy comprising Herceptin, toripalimab, and FLOT chemotherapy. The postoperative pathological findings showed mild atypical hyperplasia of the local glands with chronic mucosal inflammation (proximal stomach), no clear residual tumor (tumor regression grade 0), no regional lymph node metastasis, and

negative upper and lower cut ends. The levels of tumor markers were reduced to normal levels after re-examination. With good postoperative recovery, the four-cycle preoperative chemotherapy was continued at the same dosage as that previously administered. After the treatment, the patient was monitored every 3 mo with a follow-up of 12 mo (4 times). As of February 27, 2022, he was in a good condition without disease progression. The clinical trial registration number is E2019401.

### CONCLUSION

There are many ongoing studies on neoadjuvant immunotherapy combined with chemotherapy or radiotherapy; however, most of these studies are phase II studies with small cohorts. According to the results of some current studies, these combined regimens have shown promising results in terms of efficacy and safety. However, the clinical efficacy and safety of the neoadjuvant therapies used in these combined regimens need to be confirmed by additional prospective phase III clinical trials, and further exploration of molecular markers for effective populations is required.

**Key Words:** Toripalimab; Targeted therapy; Chemotherapy; Perioperative management; Gastric carcinoma; Case report

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**Core Tip:** We report a case in which pathologic complete response was achieved by neoadjuvant administration of toripalimab, Herceptin, and docetaxel, oxaliplatin, calcium folinate, and fluorouracil chemotherapy followed by surgery for human epidermal growth factor receptor 2- and programmed death-ligand 1-positive locally advanced gastric carcinoma. We hope that this case will shed some light on neoadjuvant therapy for gastric carcinoma.

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### INTRODUCTION

Gastric carcinoma has a high incidence in China. Surgery might be a radical cure for gastric carcinoma; however, it is limited to only early-stage gastric carcinoma (stage I). The 5-year survival rate of patients with locally advanced gastric carcinoma (late stage) is 30%–50% [1], even with an extended area of resection and lymph node dissection. Many studies have confirmed that the combination of adjuvant/neoadjuvant chemotherapy/chemoradiotherapy can improve patients' prognosis, enhance R0 resection rates, reduce distant metastases and recurrence rates, and improve survival rates through tumor downstaging [2-4]. In the European randomized controlled phase III AIO-fluorouracil (FLOT)-4 trial, resectable gastric carcinoma patients received either the FLOT (docetaxel, oxaliplatin, calcium folinate, and fluorouracil) or epirubicin, cisplatin, and fluorouracil (ECF) regimen before and after surgery. The results showed that the FLOT regimen had better efficacy, higher R0 resection rate, better disease-free survival (DFS), and better overall survival (OS) than the ECF regimen, which laid the foundation for the FLOT regimen to become a new standard perioperative therapy for advanced gastric carcinoma. Therefore, a regimen that combines surgery with neoadjuvant or perioperative chemotherapy has been recommended by the guidelines of the Chinese Society of Clinical Oncology, the European Society for Medical Oncology, and the National Comprehensive Cancer Network (NCCN).

The KEYNOTE-059 [5] and ATTRACTION-02 [6] trials have suggested that programmed death-1 (PD-1) inhibitors are effective for advanced gastric carcinoma/adenocarcinoma of the gastroesophageal junction. The United States Food and Drug Administration (FDA) and the National Medical Products Administration have approved the indications for pembrolizumab in patients with a programmed death-ligand 1 (PD-L1) combined positive score (CPS)  $\geq 1$  and nivolumab in the third-line and posterior-line treatment of advanced gastric carcinoma. The CheckMate-649 [7] and ATTRACTION-04 [8] trials have revealed that nivolumab plus chemotherapy has significantly better efficacy than chemotherapy alone in the first-line treatment of advanced gastric carcinoma/adenocarcinoma. In China, as the first approved immunotherapy targeting PD-1, toripalimab (JS001) induces the endocytosis of PD-1, reduces the expression of PD-1 on the membrane surface, and relieves the immunosuppression of T cells, thereby achieving strong antitumor effects. In 2020, the American Society of Clinical Oncology reported

the clinical response and biomarker analysis of first-line toripalimab combined with standard chemotherapy for solid tumors in a phase II cohort study[9]. The study found that the objective response rate (ORR) was 54.5%, the disease control rate was 84.8%, and the duration of response was 8.3 mo. Moreover, in the randomized controlled phase III KEYNOTE-585[10] trial, which is currently enrolling patients, therapy-naïve patients with locally advanced gastric carcinoma/adenocarcinoma of the gastroesophageal junction in the experimental group will receive pembrolizumab combined with neoadjuvant chemotherapy before surgery and pembrolizumab combined with adjuvant chemotherapy after surgery, whereas those in the control group will receive placebo combined with chemotherapy.

Human epidermal growth factor receptor 2 (HER2), also known as erythroblastic oncogene B2 (ERBB2), is a proto-oncogenic protein encoded by the *ERBB2* gene on human chromosome 17. Tyrosine kinase receptor that binds to the membrane is a protein product of this gene. This receptor can promote cell proliferation and inhibit apoptosis, leading to neoplasm formation[11]. *HER2* overexpression or amplification is found in 13%–22% of patients with gastric carcinoma or adenocarcinoma of the esophagogastric junction[12]. Immunohistochemistry (IHC) staining and fluorescent *in situ* hybridization (FISH) are recommended by the guidelines for the detection of *HER2* overexpression in patients with advanced gastric adenocarcinoma. In 2010, trastuzumab was approved by the FDA as a first-line drug in combination chemotherapy for *HER2*-positive gastric carcinoma. In another study[13], preliminary results were obtained for combined immunotherapy, trastuzumab, and chemotherapy for gastric carcinoma/esophageal cancer/adenocarcinoma of the esophagogastric junction. The study found that the 6-mo progression-free survival (PFS) rate was 75%, the ORR was 91%, the median PFS was 13 mo, and the median OS was 27.3 mo. The above data were better than the previous data for *HER2*-positive advanced gastric carcinoma.

In this study, we report a case in which pathologic complete response (pCR) was achieved by neoadjuvant toripalimab, Herceptin, and FLOT chemotherapy followed by surgery for *HER2*- and PD-L1-positive locally advanced gastric carcinoma. We hope to provide more evidence for neoadjuvant therapies in gastric carcinoma patients by reporting this case.

## CASE PRESENTATION

### Chief complaints

A 63-year-old male patient experienced dysphagia, poor appetite, night sweats, and fatigue on July 2, 2020, and sought medical attention at the Hulunbuir People's Hospital in Inner Mongolia, China.

### History of present illness

On July 22, 2020, gastroscopy revealed protuberant lesions in the cardia and fundus; bite biopsy revealed adenocarcinoma of the cardia (Figure 1A); IHC revealed *HER2* positivity (2+, FISH was recommended); *in situ* hybridization revealed *EBER* (–); and FISH revealed *HER2* positivity (Figure 1B).

### History of past illness

The patient has been suffering from hepatitis B virus (HBV) infection for more than 30 years, without history of hypertension, coronary heart disease, diabetes, or tuberculosis.

### Personal and family history

The patient's family history is not applicable.

### Physical examination

The tissues obtained from the bite biopsy were tested for PD-1, revealing CPS positivity (CPS = 1) (Figure 1C) and TPS negativity.

### Laboratory examinations

On July 22, 2020, gastroscopy revealed protuberant lesions in the cardia and fundus; bite biopsy revealed adenocarcinoma of the cardia; IHC revealed *HER2* positivity (2+, FISH was recommended); *in situ* hybridization revealed *EBER* (–); and FISH revealed *HER2* positivity. Next-generation sequencing (NGS) revealed tumor protein p53 (*TP53*) c.329G>C p.Arg110Pro (abundance 33.82%), and *ERBB2* copy number amplification ( $n = 4.5$ ).

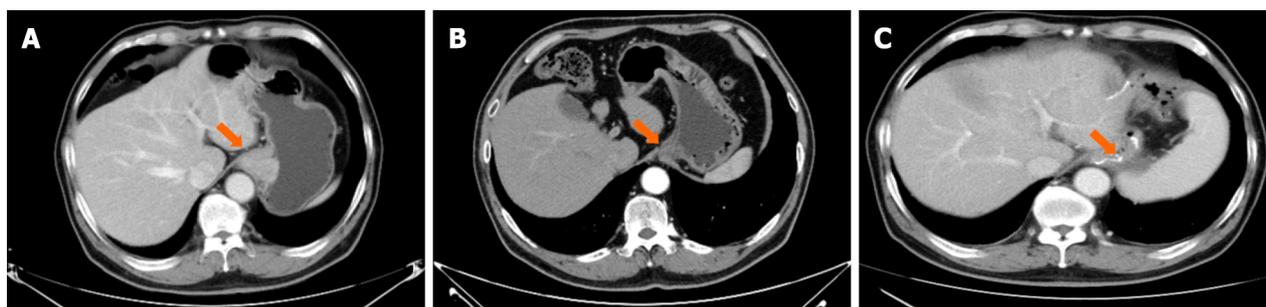
### Imaging examinations

On July 30, 2020, a computed tomography (CT) scan was performed (Figure 2A).



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**Figure 1 Histology and immunohistochemistry images.** A: Histology; B: Positivity for programmed death-ligand 1 (combined positive score = 1); C: Positivity for human epidermal growth factor receptor 2.



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**Figure 2 Computed tomography images.** A: Baseline; B: After neo-adjuvant therapy; C: After surgery.

## FINAL DIAGNOSIS

(1) Thickened wall of the cardia and adjacent lesser curvature of the stomach, suggestive of carcinoma of the cardia, and invaded fundus and multiple lymph nodes in the hepatogastric ligament region, for which clinical and endoscopic examination needed to be performed; (2) Multiple cysts in the liver; (3) Cyst of the right kidney; (4) Slightly thickened left adrenal gland, with follow-up visits recommended; (5) Prostatic calcification; (6) Subpleural ground-glass opacity in the right lung and scattered nodules and granules on the pleura of both lungs and under the interlobar pleura, with follow-up visits recommended; and (7) A dot-like compact shadow on the 5<sup>th</sup> right rib, for which follow-up visits were recommended.

## TREATMENT

From July 30, 2020 to September 2020, four-cycle targeted therapy, chemotherapy, and immunotherapy were administered. The specific regimen was as follows: Trastuzumab: 420 mg in the first cycle and 280 mg in the second cycle; docetaxel: 90 mg, ivd, d1; oxaliplatin: 150 mg, ivd, d1; calcium folinate: 700 mg, ivd, d1; fluorouracil: 4800, civ, 46 h; and toripalimab: 240 mg, ivd, d2; Q2W. Grade I gastrointestinal reaction occurred and improved after symptomatic treatment.

The imaging findings (CT on October 15, 2020, compared with that on July 30, 2020) after the four cycles of therapy were as follows (Figure 2B): The wall thickness of the cardia and adjacent lesser curvature was less than that before therapy; lymph nodes in the hepatogastric ligament region were reduced in size; and subpleural infiltration in the right lower lobe was more absorbed. No other significant changes were noted. Upper gastrointestinal tract radiography revealed carcinoma of the cardia.

Under general anesthesia, the patient underwent laparoscopic radical D2 gastrectomy for gastric carcinoma on October 23, 2020. Surgical findings revealed a neoplasm at the fundus of the stomach from the cardia, which presented as a 4 cm × 2 cm ulcer with local serosal invasion. No significantly enlarged lymph nodes were found around the stomach. The lesions presented post-chemotherapy scar-like changes. Multiple small lymph nodes were noted around the stomach, most of which were post-chemotherapy changes. The postoperative pathological findings revealed focal (proximal stomach) mild atypical glandular hyperplasia with chronic mucosal inflammation, no clear residual tumor (tumor

regression grade 0), no regional lymph node metastasis, and negative upper and lower cut ends. The grading was as follows: Station 1 0/9, Station 2 0/6, Station 3A 0/12, Station 3B 0/2, Station 4SA soft tissue (-), Station 4SB 0/1 and soft tissue (-), Station 4D 0/2, Station 5 soft tissue (-), Station 6 0/1, Station 7 soft tissue (-), Station 8 soft tissue (-), Station 9 0/4, Station 12A soft tissue (-), Station 19 0/1, and Station 20 0/2. No circulating tumor microemboli or circulating tumor cells were detected. A retest of tumor markers showed a return to normal levels.

## OUTCOME AND FOLLOW-UP

With good postoperative recovery, the postoperative CT film (performed on November 16, 2020, [Figure 2C](#)) was stored, and the four-cycle chemotherapy regimen was continued at the same dosage as that administered previously. Until February 27, 2022, the patient was examined quarterly for 12 mo (4 times), and he was in a good condition without disease progression. The timeline of this case report is indicated in [Figure 3](#).

## DISCUSSION

In a study of combined immunotherapy and trastuzumab treatment for HER2-positive gastric carcinoma[13], 25 patients received immunotherapy and targeted therapy as the initial treatment and chemotherapy in the second cycle, whereas 12 patients received immunotherapy, targeted therapy, and chemotherapy as the initial treatment. In the initial treatment, no significant difference was observed in PFS and 12-mo OS between the 25-patient and 12-patient groups. While in our case, the patient did not receive chemotherapy in the initial treatment; more specifically, the patient received Herceptin and toripalimab in the first cycle and chemotherapy in the second cycle. Previous studies have found no difference in survival between groups receiving chemotherapy and groups not receiving chemotherapy in the initial treatment. Our study suggested that, for HER2-positive gastric carcinoma patients, it is worthy to further evaluate whether the first-line “de-chemotherapy” can be carried out with a large cohort sample.

It is believed that the basis for immunotherapy to benefit HER2-positive patients is that trastuzumab induces antibody-dependent cell-mediated cytotoxicity, improves the presentation of tumor antigens, and paves the way for immune reaction of tumors[14]. Clinical data also show that HER2-positive breast cancer has more types of tumor-infiltrating lymphocytes than average, which demonstrates the importance of trastuzumab in immunity induction[15]. In addition, studies have confirmed that trastuzumab can increase the expression level of PD-L1 in immune cells of patients with breast cancer [16]. Combined with the encouraging clinical outcome of this patient, it is promising to investigate the systemic immune responses in depth, for instance, the lymphocyte infiltration, immune marker dynamics, and functional cytokine secretion. Moreover, this patient has been infected with HBV for many years, which may have an impact on his immune system. Large cohorts are necessary to draw conclusions regarding this aspect if feasible.

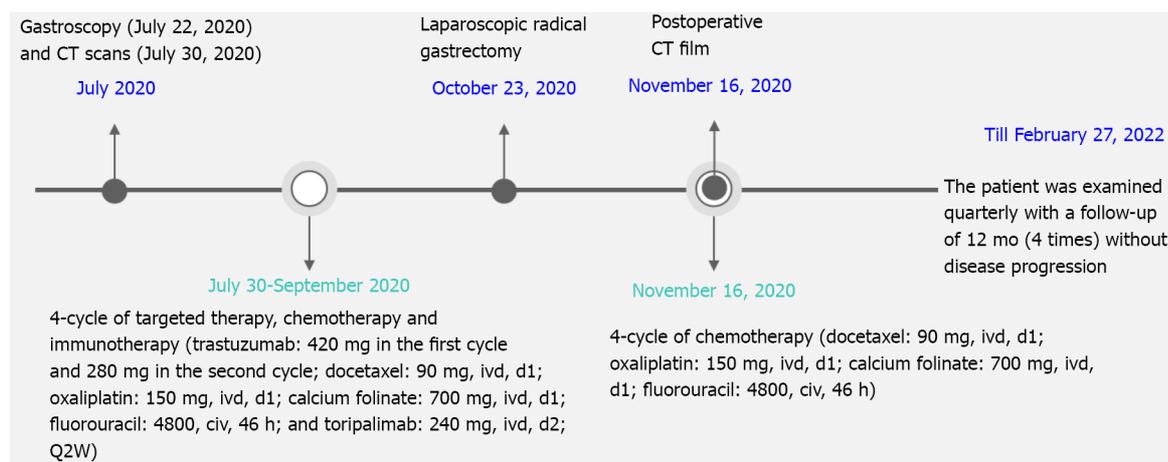
There are many ongoing studies of neoadjuvant immunotherapy combined with chemotherapy or radiotherapy; however, most of these studies are phase II studies with small cohorts. According to some of the results reported thus far, these combined regimens have shown promising efficacy and safety[17-19] ([Table 1](#)). Many studies have shown that chemotherapy can: (1) Boost the release of damage-associated molecular patterns from tumor cells and improve tumor cell immunogenicity; and (2) Elevate the levels of major histocompatibility complex molecules and enhance tumor antigen presentation[20]. Additionally, chemotherapy promotes the expression of PD-1/PD-L1 through a variety of signaling pathways. Therefore, in this case, chemotherapy and immunotherapy were applied for the patient before the surgical removal. For gastric carcinoma, first-line immunotherapy combined with chemotherapy is recommended by NCCN guidelines for patients with a PD-L1 CPS  $\geq 5$ . However, the CheckMate 649 study[7] suggested that nivolumab combined with chemotherapy improves the OS and DFS of all patients, including those with a CPS  $\geq 5$  and CPS  $\geq 1$ . In line with this, our patient's IHC results revealed PD-L1 with a CPS of 1. More prospective cohort studies are needed to determine the selection of biomarkers in neoadjuvant therapies involving immunotherapy and chemotherapy.

Apart from the above aspects, *TP53* is a crucial tumor suppressor gene, and *TP53* mutation occurs at an incidence of approximately 45% in gastric carcinoma[21]. The efficacy of immunotherapy varies with the *TP53* mutation. According to the retrospective meta-analysis mentioned above, *TP53* mutation was negatively correlated with the patients' OS with either colon cancer or gastric carcinoma who received immunotherapy but was positively correlated with the efficacy of immunotherapy for lung cancer[21]. In this study, *TP53* c.329G>C p.Arg110Pro mutation was detected using NGS in the baseline tissues of the patient. Therefore, additional prospective cohort studies are required to conclude and explore the correlation between *TP53* mutation and the efficacy of immunotherapy for gastric carcinoma.

**Table 1 Summary of neoadjuvant immunotherapies for gastric carcinoma**

Regimen	Neoplasm	Number of participants	pCR rate	MPR	Ref.
Camrelizumab plus FOLFOX	Locally advanced gastric carcinoma and adenocarcinoma of the esophagogastric junction	26	2 (9%)	8 (36%)	[17]
Sintilimab plus FLOT	Gastric and adenocarcinoma of the esophagogastric junction	17	3/17 (17.6%)	10/17 (58.8%)	[18]
Sintilimab plus CapeOX	Locally advanced resectable gastric/adenocarcinoma of the esophagogastric junction	26	6/26 (23.1%)	14/26 (53.8%)	[19]

MPR: Mannose 6-phosphate receptors; pCR: Pathologic complete response.



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**Figure 3 Timeline of this case report.** CT: Computed tomography.

## CONCLUSION

Here, we demonstrated that in a patient with HER2-positive locally advanced gastric carcinoma, there was scope for resection; therefore, a regimen composed of Herceptin, chemotherapy, and immunotherapy was carefully selected to achieve higher efficacy and better surgical resection. The patient was administered with the perioperative regimen comprising Herceptin, FLOT, and toripalimab. The postoperative pathological findings revealed that this regimen led to complete tumor response and the levels of tumor biomarkers returned to normal. Furthermore, no circulating tumor cell was detected and no significant immune-related adverse effects were noted, demonstrating that this regimen had sufficient efficacy and safety. The four-cycle chemotherapy was continued postoperatively and completed in the patient, in line with the principle of "effective treatment should be continued if the symptoms are relieved". This patient is currently in the quarterly follow-up period. A previous study suggested that the ability to achieve postoperative pCR in patients with neoadjuvant therapy is positively correlated with longer durations of survival[22]. Thus far, all tumors have been removed from this patient using this regimen, and we hope that this regimen will lead to long-time survival benefits.

## FOOTNOTES

**Author contributions:** Liu R designed the experiments, processed the data, applied for fund support, and wrote the first draft; Wang X performed the data collection; Ji Z, Deng T, Li HL, Zhang YH, Yang YC, Ge SH, Zhang L, Bai M and Ning T performed the data analysis; Ba Y modified the article.

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