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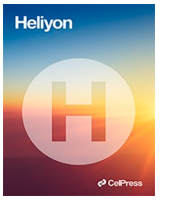

Case report

Significant effect of posterior line treatment of HER2 positive advanced gastric cancer: A case report

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ABSTRACT

At present, there are few options for third line and above treatment of advanced gastric cancer and the single drug effect is poor. HER2 positive gastric cancer is an important subtype of gastric cancer and has certain immune characteristics. The combination of HER2 inhibitor and PD-1 inhibitor has a synergistic effect, and anti-tumor drugs targeting HER2 can play an anti-angiogenesis role by downregulating VEGF. We report a patient with HER2-positive gastric cancer who developed post-operative tumor recurrence and metastasis after adjuvant chemotherapy and radiotherapy. Trastuzumab combined with albumin paclitaxel was used as second-line treatment with progression-free survival for 9 months. In third line treatment, we retained trastuzumab and combined it with camrelizumab and apatinib. During the treatment period, although the patient stopped taking the drugs due to the side effects of camrelizumab and apatinib, he achieved a PFS of 10.4 months. Considering the good effect of the third line treatment, we added another PD-1 inhibitor and continued to combine trastuzumab treatment. We found that the patient still benefited from the treatment and continued to survive for another 4 months. At present, the patient is treated with DisitamabVedotin (HER2-ADC) combined with PD-1 inhibitor, and no overall survival outcome has been observed.

1. Introduction

Gastric cancer is the fifth malignant tumor worldwide and the second largest cause of cancer-related death [1]. Despite recent advances in the treatment of gastric cancer, the mortality rate remains high. Surgery and chemotherapy are the basic treatment methods. The emergence of targeted therapy and immunotherapy will help to improve the prognosis of patients. Among them, HER2-positive gastric cancer is an important subtype of gastric cancer. The prognosis of patients with HER2-positive gastric cancer is worse, and the heterogeneity of HER2 expression is a poor prognostic factor [2,3]. Current research shows that the positive rate of HER2 differs in different Lauren types and locations of gastric cancer. HER2 expression is also different in tumors of the same patient [4]. Although the use of trastuzumab has greatly improved the progression-free survival (PFS) and overall survival (OS) of patients, for

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patients with HER2-positive gastric cancer, the therapeutic effect of trastuzumab is far less than that of breast cancer. Therefore, the treatment of HER2-positive gastric cancer needs to be further explored. In recent years, the research breakthrough of immunotherapy as first-line treatment field of gastric cancer has confirmed the use of immunotherapy in gastric cancer. Studies have shown that HER2-positive gastric cancer can show certain immune characteristics. Initial results of the use of immunotherapy in patients with HER2 positive gastric cancer are known and immunotherapy become a research hotspot.

2. Case presentation

The case is a 52-year-old male. On July 10, 2019, gastroscopic biopsy showed poorly differentiated adenocarcinoma of the gastric antrum. On July 23, 2019, the patient underwent laparoscopy-assisted distal gastrectomy and billroth II gastrojejunostomy under general anesthesia. The postoperative pathology was poorly differentiated adenocarcinoma. Lauren's classification was diffuse type. The tumor penetrated the serosa layer of the gastric wall and invaded the surrounding pancreatic tissue. Vascular tumor thrombi and peripheral nerve invasion were seen, involving the duodenum. Metastatic carcinoma of lymph nodes (8/51) was apparent; the pTNM stage was T4bN3a. Immunohistochemistry (IHC) images showed that 10% of tumor cells had weak to moderate basal lateral membrane, lateral membrane or complete membrane staining. IHC indicates HER2 2 + (Fig. 1), AFP (individual cells +), c-Met (−), EGFR (−), GPC3 (−), MLH1 (+), MSH2 (+), MSH6 (+), PMS2 (+), and SALL4 (partial +). The clones of the primary antibodies are 4B5 (Roche VENTANA BenchMark ULTRA), GA000807 (LEICA BOND III), SP44(Roche VENTANA BenchMark ULTRA), 5B7 (Roche VENTANA BenchMark ULTRA), 1G12 (Roche VENTANA BenchMark ULTRA), OTI4H4 (DAKO LINK48), RED2 (DAKO LINK48), EP49 (DAKO LINK48), EP51 (DAKO LINK48) and 6E3(Roche VENTANA BenchMark ULTRA). Fluorescence in situ hybridization (FISH) showed that the tumor had heterogeneity; approximately 10% of tumor cells had *HER2* amplification (HER2/CEP17 = 5.8) (see Supplementary figure). Eight cycles of adjuvant chemotherapy with SOX regimen (oxaliplatin + tegafur, gimeracil and oteracil potassium) were given after operation. Grade II neutrophils, grade I nausea and grade I neurotoxicity occurred during treatment. In May 2020, the patient received 25 doses of radiotherapy in the local hospital. On July 14, 2020, CT re-examination showed that there were multiple nodules around the lower esophagus and cardia, which were considered to be metastatic lymph nodes. Multiple low-density nodules were seen in the liver, and metastasis was considered. On July 20, 2020, the patient began to receive trastuzumab combined with albumin bound paclitaxel for eight cycles. The objective response was PR. Grade I neurotoxicity occurred during treatment. On April 2021, the curative effect was evaluated as PD after CT re-examination (Fig. 2). The patient began to receive trastuzumab + apatinib + camrelizumab every three weeks. After 2 and 4 cycles, the efficacy was determined as PR (Fig. 2). Apatinib was stopped because the patient had grade II diarrhea after the fifth cycle, accompanied by weight loss. The diarrhea was relieved after stopping the apatinib. Since the beginning of the three-drug combination regimen, the patient experienced rash and pruritus after every cycle of medication, which could be relieved by itself, but is progressively aggravated with the number of treatment sessions. Degree II oral ulcer occurred after the thirteenth cycle. Therefore, camrelizumab was discontinued in February 2022. The patient continued to receive trastuzumab for one cycle. CT re-examination showed that the liver metastasis was larger, and the curative effect was judged as PD on February 19, 2022 (Fig. 2). PFS was 10.4 months with PD-1 inhibitor, trastuzumab, and tyrosine kinase inhibitor (TKI). Considering that the patient might benefit from a PD-1 inhibitor, four cycles of treatment with tislelizumab (Fc segment modified PD-1 antibody) combined with trastuzumab were initiated in March 2022. The best response was PR and no adverse reactions occurred. CT re-examination showed thickening of the intestinal wall of the ascending colon, which was considered as PD on July 6, 2022. The replacement regimen was disitamab + vedotin combined with tislelizumab for 2 cycles and no significant adverse reactions occurred. At present, the first efficacy evaluation has been completed, and it was SD. The patient's PFS for third-line treatment was 10 months. The patient has survived 38 months since radical operation, 26 months since metastasis and 17 months since (Fig. 3).

3. Discussion

HER2 positive gastric cancer is a special type of gastric cancer. HER2 is located on human chromosome 17q21 and is the second member of the epidermal growth factor receptor family. Normally, HER2 is expressed at a low level in mammary glands and the skin,

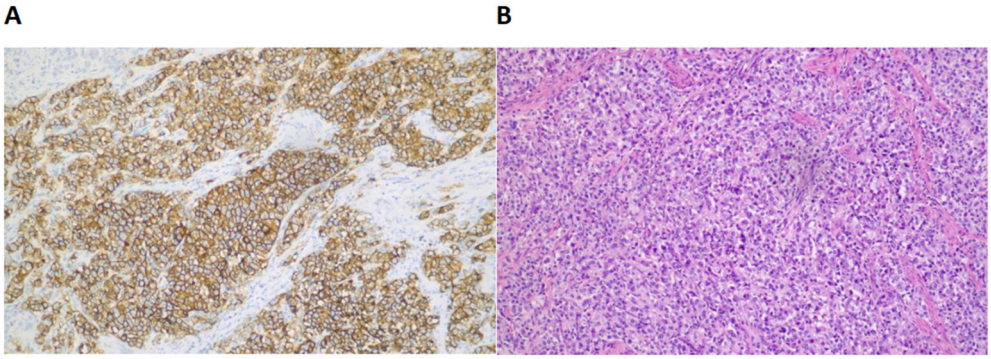

Fig. 1. A. IHC staining (magnification, × 100); B.HE staining (magnification, × 100). IHC, immunohistochemistry; HE, hematoxylin-eosin staining.

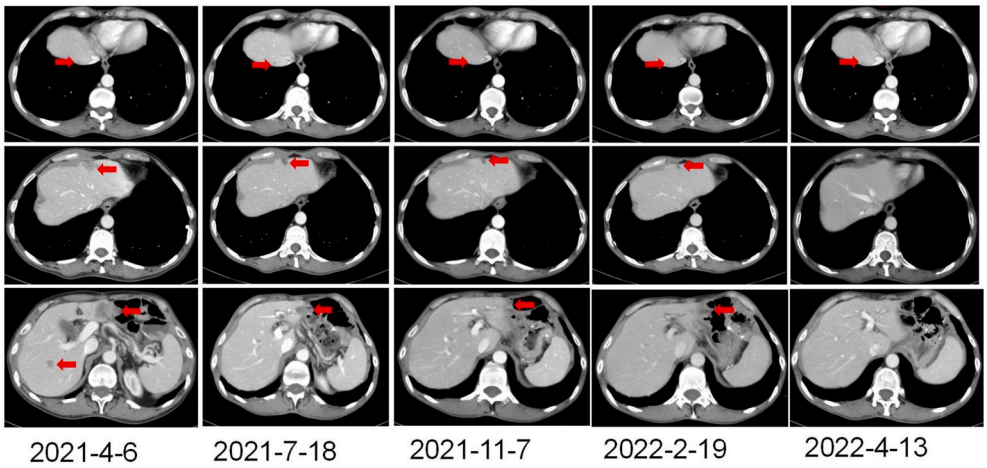

Fig. 2. Changes in CT images.

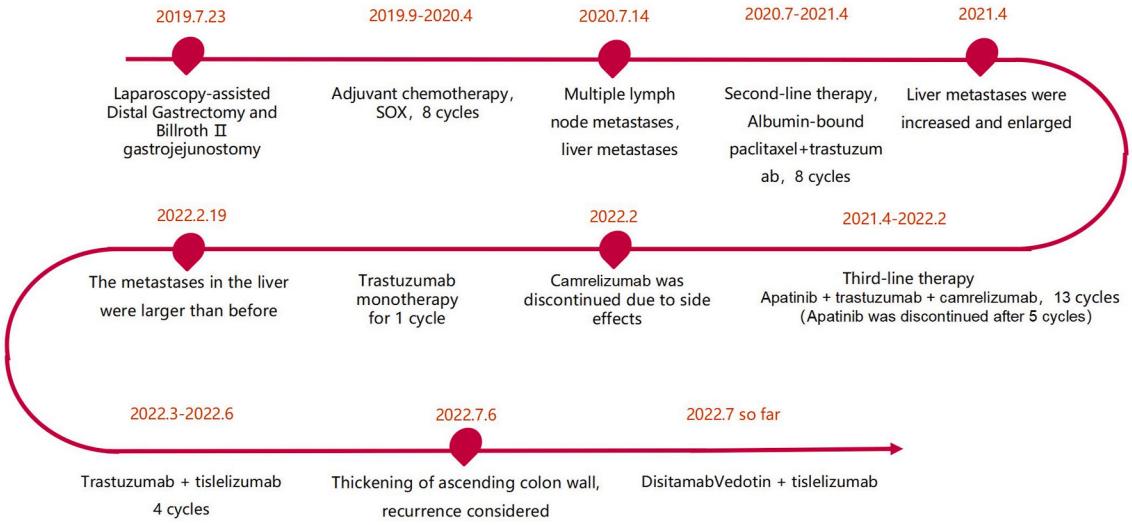

Fig. 3. Flow chart of treatment.

as well as in epithelial cells of the gastrointestinal tract, reproductive system, respiratory tract, and urethra, regulating cell growth, proliferation, and apoptosis. When HER2 is affected by carcinogenic factors, its structure or expression is activated out of control, and begins to exhibit tumor transforming activity, which can promote the malignant transformation of gastric mucosa cells. Therefore, the overall malignancy of HER2-positive gastric cancer is higher than that of HER2-negative gastric cancer. HER2-positive is defined as IHC 3+ or IHC 2+ simultaneous FISH. In the 2019 WHO Classification of Digestive System Tumors, it is recommended to test patients with gastric adenocarcinoma for HER2 as it can affect treatment decisions [5].

Studies have confirmed that the overexpression rate of HER2 in gastric cancer is 7–53.4% [6–8]. The expression of HER2 in gastric cancer is unique. Studies have shown that the positive rate of HER2 in gastric and esophageal junction carcinoma is higher than that in distal gastric cancer; the positive rate of HER2 in intestinal gastric cancer is higher than that in diffuse and mixed type gastric cancer; and the positive rate of HER2 in cancer tissues is higher than that in adjacent tissues [7]. HER2 expression in gastric cancer is usually more heterogeneous than that in breast cancer. Heterogeneity is usually seen in IHC2+ gastric cancer or mixed histology. The ToGA study, the first clinical trial of a monoclonal antibody targeting HER2 in advanced gastric cancer, showed that the overall positive rate of HER2 expression in gastric cancer tissues was 22.1%, among which the positive rates of intestinal type gastric cancer and gastroesophageal junction cancer were the highest (31.8% and 32.2%, respectively), and the positive rates of diffuse type and distal tumors were low (6.1% and 21.4%, respectively) [9]. This study also further confirmed that after first-line application of trastuzumab combined with chemotherapy compared with chemotherapy alone in patients with HER2-positive advanced gastric cancer, the median OS increased from 11.1 months to 13.8 months, and the overall response rate (ORR) increased from 35% to 47%. EVIDENCE, a non-intervention, real-world study carried out in China, showed that trastuzumab combined with chemotherapy could prolong the OS of HER2-positive metastatic gastric cancer to 22.3 months compared to chemotherapy without trastuzumab, supporting the data of the

ToGA study, and opens a new chapter in the targeted treatment of gastric cancer at the level of individualized treatment [10].

In recent years, immunotherapy has gradually become a research hotspot in the field of tumor therapy, and is also the development direction of tumor translational medicine. The advent of tumor immunotherapy has also brought new opportunities for the treatment of HER2-positive gastric cancer. Gall et al. have found in preclinical models that trastuzumab can mediate the presentation of HER2 antigen epitopes by dendritic cells through the Fc segment and increase the infiltration of HER2-specific T cells in the microenvironment, linking innate and adaptive immunity [11]. Studies have also confirmed the synergistic effect of trastuzumab combined with PD-1 inhibitor [12]. There is an increasing number of clinical trials assessing the combination of immunity and targeting. Margetuximab is a monoclonal antibody targeting HER2 modified by the Fc segment. In first-line treatment of HER2 and PD-L1 double positive gastric cancer patients, the combination of margetuximab with the PD-1 inhibitor retifanlimab achieved an ORR of 52.5%, with 10% of patients achieving complete remission [13]. The first interim analysis of the KEYNOTE-811, reported at the 2021 ASCO annual meeting, pembrolizumab combined with trastuzumab and chemotherapy can increase the ORR to 74.4% and disease control rate (DCR) to 96.2% in patients with HER2-positive advanced gastric cancer. Therefore, the regimen of pembrolizumab combined with trastuzumab and chemotherapy was also approved by the Food and Drug Administration (FDA) and has become a new therapy for the first-line anti-HER2 treatment of gastric cancer. The primary endpoints OS and PFS need to be further analyzed [14].

The case described in this study had tumor recurrence and metastasis after adjuvant chemotherapy and radiotherapy. The second-line treatment progressed after 9 months of trastuzumab combined with albumin-bound paclitaxel treatment. At present, there are few options for third line and above treatment of advanced gastric cancer. The Chinese Society of Clinical Oncology (CSCO) approved apatinib (a TKI of VEGFR), nivolumab (a PD-1 inhibitor), and irinotecan (a single drug) for posterior line treatment of gastric cancer. However, the PFS of the above drugs alone did not exceed 3 months. For patients previously treated with trastuzumab, the choice of posterior line treatment is inconsistent. In recent years, clinical trials are testing the effects of combining different drugs to further improve the treatment status of patients with gastric cancer who failed to receive standard treatment. Patients with gastric cancer are relatively weak, and most cannot tolerate chemotherapy for a long time. In a study of a chemo-free regimen, TKI combined with PD-1 inhibitor may have a synergistic effect. In the Phase Ib REGONIVO study, regorafenib combined with nivolumab was used to treat patients with advanced gastric and colorectal cancer. The overall ORR reached 40%, and the PFS of gastric cancer patients in 12 months reached 22.4%, showing encouraging anti-tumor activity [15]. Other studies on PD-1/PD-L1 inhibitors combined with TKI are ongoing. Apatinib is a small molecule anti-angiogenesis drug independently developed in China, which has been shown to be safe and effective in the treatment of advanced gastric cancer. In a retrospective study in China, apatinib combined with PD-1 inhibitor achieved better efficacy than apatinib or PD-1 inhibitor alone, and HER2-positive patients seemed to benefit more [16]. At present, Apatinib has not been marketed in other countries, has not been put into clinical use, and is still under research.

At present, there are many studies on the correlation between PD-L1 and HER2 expression. Yamashita et al. considered that trastuzumab could upregulate the expression of PD-L1 in gastric cancer cells by interacting with NK cells [17]. Suh et al. found that inhibiting the EGFR/HER2 signaling pathway downregulated the expression of PD-L1 [18]. Oki et al. showed that 72.4% of HER2 3+ patients exhibited high expression of PD-L1, and small interfering RNA-mediated HER2 downregulation significantly reduced the expression of PD-L1 in the gastric cancer cell line MKN45. At present, there are other different views [19]. Chaganty et al. suggested that trastuzumab may release interferon (IFN)-γ by interacting with immune effector cells, and upregulate the expression level of PD-L1, which may also contribute to trastuzumab resistance. Inhibition of HER2 downstream signaling downregulates PD-L1 expression [20]. Although the correlation between the status of PD-L1 and expression of HER2 remains unclear, many studies have confirmed the positive regulatory effect of HER2 inhibitors on the tumor immune environment. Studies have confirmed that inhibition of the HER2 pathway can cause release of cytokines such as CCL2, CCL21, VEGF, and CXCL1, and create a more favorable environment for tumor immunotherapy [21]. Trastuzumab combined with pembrolizumab can enhance the specific T cell response of HER2, promote the transport of T cells and dendritic cells, and induce the expansion of peripheral memory T cells [22–24]. This suggests the potential value of adding anti-PD-1 or anti-PD-L1 to trastuzumab basic treatment. In the retrospective ATTRACTION-2 study, researchers took whether trastuzumab was used before enrollment as the standard to judge HER2 status and divided patients into HER2-positive and HER2-negative subgroups. The OS benefit of HER2-positive patients using nivolumab was more obvious (8.3 vs. 4.8 months) and the ORR was higher (16.9% vs. 7.7%), suggesting HER2-positive gastric cancer patients who had previously used trastuzumab were more likely to benefit from PD-1 antibody treatment [25]. There is also evidence that angiogenesis and increased VEGF expression in tumors are closely related to the overexpression of HER2 in tumor cells, and HER2-positive tumor cells are often accompanied by high expression of VEGF2 [26]. Izumi et al. showed that anti-tumor drugs targeting HER2 can play an anti-angiogenesis role by downregulating VEGF. However, this effect is transient, and host stromal cells can compensate for this effect by producing VEGF [27]. Therefore, targeting HER2 alone may not be sufficient to inhibit VEGF-mediated angiogenesis. Singh et al. confirmed the combined targeting of HER2 and VEGF has a synergistic antitumor effect [28]. Apatinib is a small molecule TKI that highly selectively inhibits VEGFR2 tyrosine kinase activity, blocks signal transduction after VEGF binding, and thus strongly inhibits tumor angiogenesis. And studies have confirmed that Apatinib can only block tumor growth *in vivo* models, confirming that its antitumor activity is mainly due to its blocking effect on angiogenesis [29]. Based on the above mechanism, apatinib combined with trastuzumab may have a synergistic antitumor effect. Therefore, in the third-line treatment of this patient, considering the synergistic effect between drugs and no overlap of the main adverse reactions, we reserved trastuzumab, and combined it with camrelizumab and apatinib to obtain 10.4 months of PFS. Considering the positive effects of third-line treatment, we replaced the PD-1 inhibitor and continued to combine it with trastuzumab. We found that patient still benefited from the treatment, with a PFS of 4 months. The patient is currently being treated with disitamab + vedotin combined with PD-1 inhibitor.

4. Conclusions

HER2-positive gastric cancer can inhibit the anti-tumor immune response by blocking the monitoring of abnormal DNA produced by cancer cells by the immune system. Anti-HER2 therapy can improve the immunosuppressive factors of the tumor microenvironment by downregulating the release of cytokines and may benefit from immune checkpoint inhibitor therapy. HER2 overexpression is closely related to the increase in VEGF expression. The synergistic effects of HER2 and VEGF inhibitors may further improve the anti-tumor activity. At present, chemo-free therapy combination therapy has been gradually explored in a variety of tumor species, but there are no large-scale randomized control results that can provide data support for posterior line HER2-positive gastric cancer patients. A prospective study to confirm the efficacy of HER2 inhibitor combined with PD-1 inhibitor and TKI is needed to provide a basis for clinical diagnosis and treatment.

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Departments of Ethics Committee, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Availability of data and materials

The references supporting the conclusions of this article is included within the article.

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CRediT authorship contribution statement

Xiaoting Ma: Conceptualization, Data curation, Writing – original draft. **Liyan Xue:** Methodology, Resources. **Kai Ou:** Formal analysis. **Xiu Liu:** Investigation. **JunLin Chen:** Project administration. **Lizhen Gao:** Supervision. **Lin Yang:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Personal contribution

XTM designed the article form and wrote the manuscript. LYX provided pathologically relevant guidance. KO and XL consulted and browsed the literature. JLC and LZG collected and followed up patient information. LY revised the manuscript. All authors read and approved the final manuscript.

Abbreviations

HER2	human epidermal growth factor receptor 2
PD-1	programmed death 1
PD-L1	programmed cell death-ligand 1
PFS	progression free survival
OS	overall survival
IHC	immunohistochemistry
TKI	tyrosine kinase inhibitor
PD	progressive disease
PR	partial remission
SD	stable disease
ORR	objective response rate
DCR	disease control rate

ASCO	American Society of Clinical Oncology
EGFR	epidermal growth factor receptor
FISH	fluorescence in situ hybridization
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
4B5	VENTANA anti-HER2/neu Rabbit Monoclonal Primary Antibody
GA000807	AFP Poly (Adp-Ribose) antibody
SP44	CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody
5B7	CONFIRM anti-EGFR(5B7) Rabbit Monoclonal Primary Antibody
1G12	Mouse Monoclonal Glypican 3 Antibody (1G12 + GPC3/863)
OTI4H4	MLH1 Mouse monoclonal antibody
RED2	MSH2 Rabbit monoclonal antibody
EP49	MSH6 Rabbit monoclonal antibody
EP51	PMS2 Rabbit monoclonal antibody
6E3	SALL4 (6E3) Rabbit Monoclonal Primary Antibody

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28923.

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