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Case Report

Long-Term Complete Response to Trastuzumab Deruxtecan in a Case of Unresectable Gastric Cancer

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Keywords
Trastuzumab deruxtecan · HER2-positive gastric cancer · Ascites

Abstract
Introduction: Trastuzumab deruxtecan (T-Dxd) has been approved for the treatment of HER2-positive gastric cancer. However, there are only a limited number of cases of gastric cancer where a long-term complete response (CR) has been maintained. Consequently, we report a case of gastric cancer in which long-term CR was maintained. ***Case Presentation:*** A woman in her late 60s underwent a gastrointestinal endoscopy, which revealed a type 2 lesion with ulceration in the lesser curvature of the vestibule, and a biopsy, which revealed an adenocarcinoma. Computed tomography (CT) revealed wall thickening of the gastric antecubital region, metastatic liver tumor, and extra-regional lymph node metastasis; a diagnosis of T4a, N3a, M1 (H, LYN), and cStage IVB (HER2 3+) was confirmed. Trastuzumab, oxaliplatin, and S-1 were administered initially. After 9 months, ascites appeared, and progressive disease was diagnosed. Paclitaxel and ramucirumab were started as second-line treatments but discontinued owing to neutropenia and increasing ascites. Third-line treatment with T-Dxd was initiated, and 11 months later, CT showed the disappearance of metastases. Even after 31 months, the CR was maintained. ***Conclusion:*** To the best of our knowledge, this is one of the few cases in which long-term CR was maintained with third-line T-Dxd treatment. Treatment strategies for patients with gastric cancer to achieve long-term CR require careful consideration.

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Introduction

Antibody-drug conjugates (ADC) are biopharmaceuticals that use a linker to link alternating carriers and cytotoxic drugs. Therefore, high therapeutic efficacy and wide safety margin can be expected by using antibodies as carriers to maximize the efficacy of the drug at the target. Human epidermal growth factor receptor 2 (HER2), a protein involved in cancer cell proliferation, is overexpressed in approximately 20% of breast and gastric cancers and associated with poor prognosis and recurrence [1]. Trastuzumab deruxtecan (T-Dxd) is an ADC of a monoclonal anti-HER2 antibody and topoisomerase I inhibitor. T-Dxd is reportedly effective against not only HER2-positive breast cancer but also low-HER2-positive breast cancer and is widely used in breast cancer treatment [2, 3].

T-Dxd has been reported to be useful for the treatment of gastric cancer. For example, the DESTINY-Gastric01 trial reported the benefits of T-Dxd in HER2-positive gastric cancer, and T-Dxd was approved in Japan in 2020 [4]. However, there are only a limited number of cases in which a long-term complete response (CR) has been maintained. Herein, we report a case of gastric cancer in which long-term CR was maintained.

Case Presentation

A woman in her late 60s consulted a local doctor owing to anemia. Her medical history included hypertension and refluxed esophagitis. The patient was referred to our hospital after an upper gastrointestinal endoscopy by her previous physician revealed a gastric tumor. Upper gastrointestinal endoscopy at our hospital revealed a type-2 lesion measuring 20 mm with an ulcer in the lesser curvature of the gastric antrum, and a biopsy revealed the presence of well-differentiated adenocarcinoma (tub1) (Fig. 1a). Computed tomography (CT) showed a tumor in the antrum and bulky lymph nodes with a minor radius of 30 mm in the lesser curvature and intramesenteric lymph nodes on the ventral side of the left kidney (Fig. 1b, c). Positron emission tomography revealed significant accumulations, with an SUVmax of 4.4 in liver S4 and 7.2 in the lesser curvature lymph nodes (Fig. 1d). The diagnosis was T4a, N3a, M1 (H, LYN), and stage IVB, according to the 8th International Union Against Cancer (HER2 immunohistochemistry: 3+) [5]. First-line treatment with trastuzumab plus S-1+oxaliplatin (trastuzumab, 8 mg/kg; oxaliplatin, 130 mg/m^2; S-1, 100 mg/body) was initiated (Table 1). Grade 3 diarrhea and Grade 2 anorexia were observed from day 8 to day 10, which improved with loperamide (3.0 mg/body) and dexamethasone (2.0 mg/body). A one-step dose reduction (trastuzumab, 6 mg/kg; oxaliplatin, 100 mg/m^2; S-1, 80 mg/body) was performed in two courses owing to diarrhea and anorexia. CT for efficacy evaluation after three courses of primary treatment showed improvement in wall thickening in the gastric antecubital region and a reduction in the size of metastatic lymph nodes (lesser curvature lymph node, 16 mm), resulting in a judgment of partial response (Fig. 2).

Although oxaliplatin was discontinued on the 12th course owing to Grade 3 peripheral neuropathy, trastuzumab and S-1 were subsequently administered. However, a CT scan conducted 9 months after treatment initiation revealed the presence of ascites and pelvic disseminated nodes, leading to a diagnosis of progressive disease (Fig. 3). Second-line treatment was initiated with paclitaxel (PTX) (80 mg/m^2) and ramucirumab (8 mg/kg). After 8 days of PTX + ramucirumab treatment, Grade 4 neutropenia was observed and treated by injecting granulocyte colony-stimulating factor (75 μg). Despite one course of second-line treatment, the ascites continued to increase. Therefore, concentrated ascites reinfusion therapy was performed; 80% of the PTX dose (64 mg/m^2) was administered during the second course; however, Grade 4 neutropenia reoccurred.

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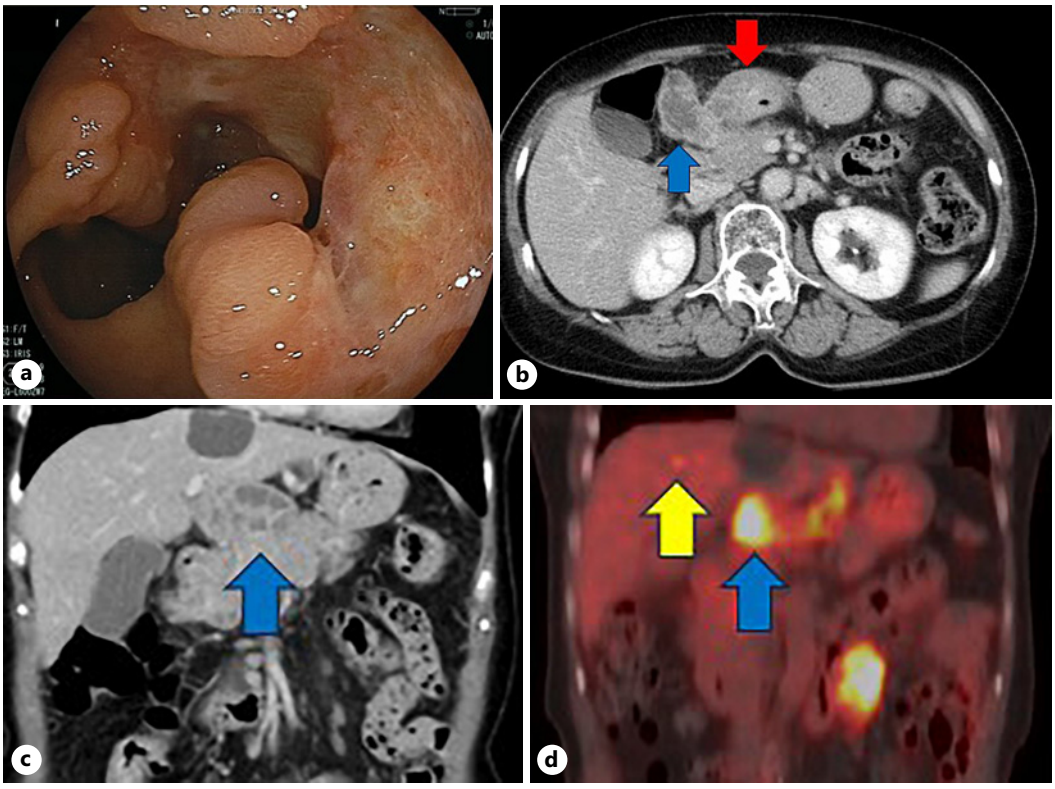

Fig. 1. Imaging examination prior to primary treatment. **a** Upper gastrointestinal endoscopy. A bulky ulcerated lesion was observed in the vestibular fontanel. Pyloric stenosis was not observed. **b** Computed tomography (CT) finding. The vestibular wall was abnormally thickened and showed hypoabsorption (red arrow), along with enlarged lesser curvature lymph nodes (blue arrow). **c** CT finding. A lymph node measuring up to 30 mm in the lesser curvature (blue arrow). **d** Positron emission tomography finding. There were significant accumulations in the lymph nodes of the lesser curvature (blue arrow) and hepatic S4 (yellow arrow).

PTX was determined to be unsustainable owing to neutropenia and increasing ascites; therefore, T-Dxd (one-step dose reduction, 5.4 mg/kg) was initiated as a third-line treatment. However, Grade 1 hepatic dysfunction due to liver metastases was observed. Therefore, we decided to perform a follow-up for the hepatic dysfunction. Since then, liver dysfunction has improved without treatment. A CT performed 2 months later showed decreased pleural effusion and partial response. Eleven months later, upper gastrointestinal endoscopy revealed scarring of the primary tumor. Thirty months later (43 courses), CT showed no apparent recurrence, and the CR was maintained (Fig. 4a). After an additional 31 months (totaling 44 courses), upper gastrointestinal endoscopy showed scarring and coverage of the primary lesion by normal mucosa. Biopsy results revealed no malignant cells (Fig. 4b).

The patient is currently receiving T-Dxd every 3 weeks, and Grade 1 anemia has been observed as an adverse event. Nevertheless, she is able to perform daily activities without problems.

Discussion

To the best of our knowledge, this is the first case of a patient with HER2-positive advanced gastric cancer who achieved a long CR with T-Dxd. Our case suggests that T-Dxd administration stabilizes advanced gastric cancer in the long term.

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Table 1. History of chemotherapy

Time order	Treatment	Best overall response
	1st line: trastuzumab + SOX was started	
After 2 months	Reduction of celiac lymph nodes was observed	PR
After 9 months	Ascites was appeared	PD
After 9 months 1 week	2nd line: PTX+RAM was started	
After 9 months 3 week	Grade 4 neutropenia was observed as an adverse event Ascites was further exacerbated	PD
After 10 months	3rd line: T-Dxd was started	
After 36 months	T-Dxd was continued	CR

CR, complete response; PD, progressive disease; PR, partial response; PTX, paclitaxel; SOX, S-1+oxaliplatin; T-Dxd, trastuzumab deruxtecan; RAM, ramucirumab.

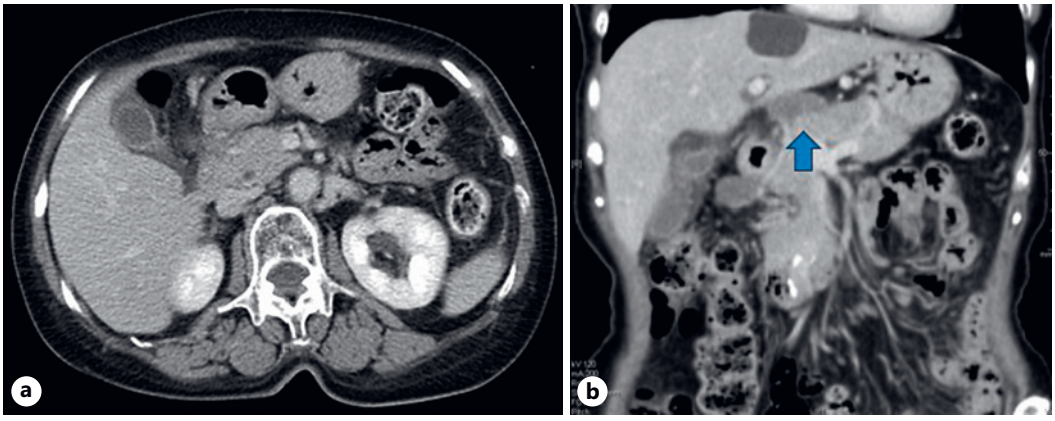

Fig. 2. CT images to evaluate efficacy 3 months after the start of primary treatment. **a** Improvement in wall thickening of the primary lesion in the vestibular area was observed. **b** The lesser curvature lymph node showed a reduction to 16 mm (blue arrow).

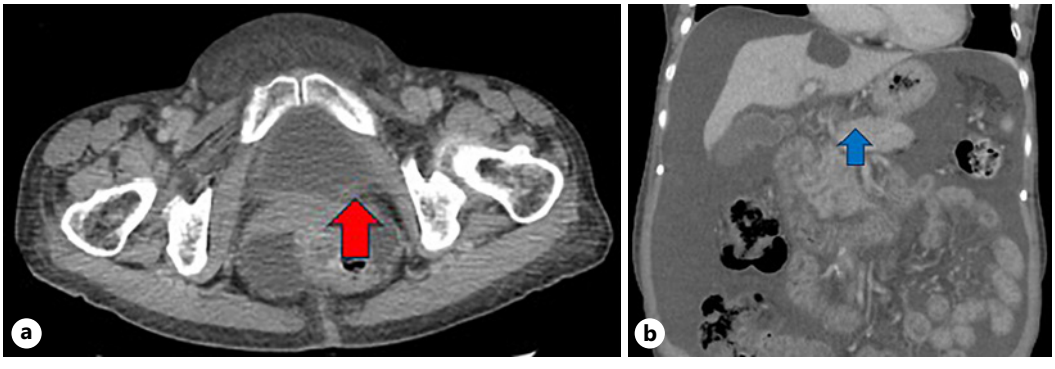

Fig. 3. CT images at the judgment of progress of disease after primary treatment. **a** The presence of pleural ascites and a pelvic dissemination site was noted (red arrow). **b** The lesser curvature lymph node had reduced in size and was no longer visible (blue arrow). Ascites was observed throughout the abdominal cavity.

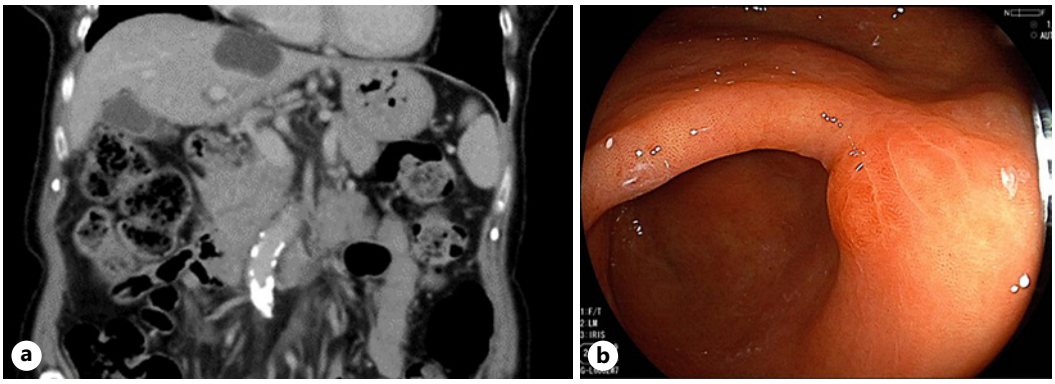

Fig. 4. Imaging examination during 3rd treatment. **a** CT finding. Ascites had disappeared, and metastatic lymph nodes had shrunk and were no longer visible. **b** Upper gastrointestinal endoscopy showed scarring of the primary lesion.

In recent years, therapeutic agents and treatments for gastric cancer involving various molecules, such as HER2 and programmed cell death protein 1, have been developed. Nivolumab, in combination with standard therapy for untreated gastric cancer, results in an improved prognosis [6]. Although there are several drugs targeting HER2-positive gastric cancer, pertuzumab and trastuzumab emtansine yielded negative trial results. Conversely, Tmab and T-Dxd have shown positive outcomes, and ongoing developments include margetuximab and others [7]. In 2010, the ToGA trial demonstrated the benefit of trastuzumab over that of conventional chemotherapy in patients with HER2-positive gastric cancer [8]. Furthermore, anti-HER2 drugs are widely used to treat gastric and breast cancers. T-Dxd is a second-generation ADC containing a DNA topoisomerase I inhibitor [9]. Several studies have investigated the mechanisms underlying the antitumor effects of T-Dxd. For example, one reported that T-Dxd is internalized into cancer cells, exhibiting antitumor activity. Additionally, it infiltrates neighboring tumor cells owing to its high membrane permeability and is expected to have a high therapeutic effect (bystander killing effect) [10]. Nakajima et al. [11] reported that T-Dxd significantly induces the mRNA expression of C-X-C motif chemokine ligands (CXCL) 9/10/11 in HER2-positive gastric cancer cells. CXCL 9/10/11 are T cell chemoattractants that recruit antitumor cytotoxic T lymphocytes via their receptor C-X-C chemokine receptor 3 and inhibit tumor progression [11]. These results indicate that T-Dxd affects not only the tumor cells but also the surrounding immune cells, indicating its antitumor action. Furthermore, the DESTINY-Gastric01 trial showed a significantly higher objective response rate in the T-Dxd group than in the conventional treatment group (42% vs. 12%); a similar trend was observed for the CR rate (10% vs. 0%) [4]. Overall survival was longer with T-Dxd than with traditional chemotherapy (median, 12.5 vs. 8.4 months). Recently, a phase II trial reported that T-Dxd is useful in gastric or gastroesophageal junction cancer with low HER2 expression after third-line treatment [12]. These trials demonstrated that the higher the HER2 expression, the better the outcomes. In our patient, the HER2 status on immunohistochemistry was 3+, consistent with the results of previous trials [4, 12]. Matsumoto et al. [13] suggested that the pre-administration of immune checkpoint inhibitors (ICI) and a sufficient trastuzumab-free interval are favorable prognostic factors for T-Dxd efficacy. While predicting treatment response with T-Dxd administration would be a valuable clinical benchmark, it has not yet been established. On the other hand, there have been reports of enhanced prognosis in cases with good PS and among male patients treated with ICIs, raising expectations for further immunological

insights [14, 15]. Molecular biological classifications have also emerged recently, including Epstein-Barr virus-positive, microsatellite instability-high, chromosomal unstable, and genomically stable categories. Notably, DNA damage response expression has been linked to a negative prognostic factor in genomically stable gastric cancer patients. These biological classifications hold potential as prognostic factors for chemotherapy and ICI outcomes in the future [16]. In our case, T-Dxd led to long-term CR; however, no clear predictive factors are known. Therefore, further studies are required to determine the prognostic factors for T-Dxd administration.

Recent advances in chemotherapy, ICIs, and molecularly targeted drugs have greatly enhanced the antitumor effects of these drugs. According to the DESTINY-Gastric01 trial, the third-line treatment, T-Dxd, showed the possibility of achieving a CR [4]. Therefore, treatment should be continued up to third-line treatment. However, the continuation rate of the third-line treatment is approximately 30% for gastric cancer, owing to rapid disease progression [17]. In our case, the cancerous ascites was uncontrollable with second-line treatment; therefore, the patient was transferred to third-line T-Dxd treatment at an early stage, and long-term CR was achieved. Consequently, conversion surgery (CS) can be considered in the future. CS has been previously performed in cases in which long-term CR was achieved using T-Dxd [18]. Yamaguchi et al. [19] classified patients with metastatic gastric cancer into four categories according to the metastatic patterns of the disease and discussed the CS and prognosis for each category (CONVO-GC). They showed that even in patients with multiple non-curative factors, the prognosis is better in those who undergo R0 resection. Thus, clinicians may consider CS when chemotherapy is successful and surgery is feasible to achieve R0 resection, even in patients with multiple non-curative factors. In our case, CS was also considered following the achievement of CR in accordance with CONVO-GC guidelines. However, our patient did not provide consent for CS due to minimal adverse events even during T-Dxd administration, promoting the continuation of third-line treatment.

The CARE checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000537845). In conclusion, we described a case in which CR was achieved using T-Dxd. Our findings imply that clinicians must determine the sequence of pharmacological treatments at the appropriate time.

Statement of Ethics

Ethical approval was not required in accordance with the local guidelines for this retrospective, unplanned study. Written informed consent was obtained from the patient for treatment and for the publication of the case and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.Y. wrote the draft and critically revised the manuscript for intellectual content. H.Y., Y.S., T.K., K.S., T.T., M.K., and M.S. contributed to the conceptualization of this report. Y.S. and T.K. diagnosed and treated the patients and interpreted and revised the results of the optical coherence tomography included in this report. H.Y. and Y.S. confirmed raw data authenticity. All the authors have read and approved the final manuscript.

Data Availability Statement

All the data generated or analyzed in this study are included in the published article. Further inquiries can be directed to the corresponding author.

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