Dramatic Response to Trastuzumab Deruxtecan Rechallenge in a Patient with HER2-Positive Gastric Cancer: A Case Report

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Patient: Male, 67-year-old
Final Diagnosis: Gastric cancer
Symptoms: Difficulty in swallowing
Medication: —
Clinical Procedure: Chemotherapy
Specialty: Oncology

Objective: Unusual setting of medical care

Background: Trastuzumab deruxtecan (T-DXd) has shown promising efficacy against human epidermal growth factor receptor 2 (HER2)-positive gastric and gastroesophageal junction (GEJ) adenocarcinomas. The efficacy of T-DXd rechallenge, however, has remained unclear. This is the first report of a dramatic response to T-DXd rechallenge in a patient with HER2-positive GEJ adenocarcinoma after confirmation of HER2 overexpression immediately prior to the rechallenge.

Case Report: A 67-year-old man was diagnosed with HER2-positive gastric cardia (or GEJ) adenocarcinoma with lymph node and liver metastases. Initial T-DXd therapy was started as fourth-line chemotherapy. The best response was partial, and progression-free survival was 5.6 months. After an immune checkpoint inhibitor-based regimen, a rechallenge with T-DXd was planned as a seventh-line treatment. HER2 overexpression was confirmed by re-biopsy immediately before the rechallenge. He is currently receiving T-DXd without progression or severe treatment-related adverse events.

Conclusions: This is the first case report of a response to T-DXd rechallenge in a patient with HER2-positive gastric cancer. This rechallenge could be considered a treatment strategy for HER2-positive gastric cancer, for cases in which the initial T-DXd treatment was effective. Confirmation of HER2 overexpression and re-biopsy immediately before the rechallenge would be important for this strategy.

Keywords: Biopsy • Stomach Neoplasms • Trastuzumab Deruxtecan

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Background

According to the ToGA study, the first-line treatment for human epidermal growth factor receptor 2 (HER2)-positive gastric cancer is trastuzumab-based chemotherapy [1]. Other anti-HER2 therapies have also been reported for HER2-positive gastric cancer, but no study, except the ToGA study, has shown the superiority of anti-HER2 therapy [2-5]. Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of a monoclonal anti-HER2 antibody and topoisomerase I inhibitor. According to the DESTINY-Gastric01 study, T-DXd results in a more promising tumor response than the physician’s choice of chemotherapy [6]. Therefore, T-DXd was approved for the treatment of HER2-positive gastric cancer in Japan in September 2020. T-DXd has now become the standard third-line chemotherapy treatment for HER2-positive gastric cancer.

Although some new drugs have also been approved for gastric cancer in recent years, anti-HER2 therapies are the most effective for HER2-positive gastric cancer. In breast cancer, trastuzumab beyond progression is one of the standard therapies, according to the GBG26/BIG03-05 study [7]. However, the T-ACT study did not show the same efficacy of trastuzumab beyond progression for gastric cancer; hence, it was not considered a standard treatment [8]. The efficacies of trastuzumab rechallenge and T-DXd rechallenge in gastric cancer remain unclear. This is the first report of a dramatic response to T-DXd rechallenge in a patient with HER2-positive gastric cancer after the confirmation of HER2 overexpression immediately prior to T-DXd rechallenge.

Case Report

A 67-year-old male patient was diagnosed with gastric carcinoma with lymph node and liver metastases. A biopsy of the primary gastric tumor was performed before first-line treatment, and a poorly differentiated adenocarcinoma was revealed. Immunohistochemistry (IHC; HercepTest, Dako, Denmark) showed the overexpression of HER2 (score=3) [9]. SOX plus trastuzumab therapy (100 mg/m² oxaliplatin intravenous [IV], 6 mg/kg trastuzumab i.v. on day 1, and 80 mg/m² S-1 p.o. on days 1-14, every 3 weeks) was started as the first-line treatment, and computed tomography (CT) imaging revealed that the disease had progressed even after 6 cycles. Paclitaxel plus ramucirumab therapy (80 mg/m² paclitaxel i.v. on days 1, 8, and 15, and 8 mg/kg ramucirumab i.v. on days 1 and 15, every month) as the second-line treatment and irinotecan therapy (150 mg/m² irinotecan i.v. on day 1, every 2 weeks) as the third-line treatment were administered, and the disease still progressed. He enrolled in a phase I trial of T-DXd, and T-DXd was started as the fourth-line treatment in August 2017. The initial dose of T-DXd was 5.4 mg/kg, and it was administered every 3 weeks. The best response was partial, and progression-free survival was 5.6 months. Subsequently, an immune checkpoint inhibitor was administered as the fifth-line and sixth-line treatments (Table 1). After the fifth-line treatment, the chemotherapy-free interval was 15.2 months because of sacral fracture due to osteoporosis. He reported difficulty swallowing during the treatment. CT and upper gastrointestinal endoscopy (UGE) revealed further progression of the primary site (Figures 1A, 2A). A re-biopsy of the primary gastric tumor was performed. IHC analysis revealed the overexpression of HER2 (score=2), and the biopsy specimen was positive on dual-color in-situ hybridization (INFORM HER2 Dual ISH DNA Probe Cocktail Assay; Figure 3A-3C). Rechallenge with T-DXd (6.4 mg/kg, every 3 weeks) was planned as the seventh-line treatment in March 2021. Laboratory data on the administration of T-DXd are summarized in Table 2. After the first cycle, the patient’s condition improved. After 3 cycles, CT showed a tumor response (Figure 1B). UGE showed shrinkage of the tumor at the primary site (Figure 2B) and HER2 overexpression was maintained after 4 cycles (Figure 3D-3F). The patient is currently receiving T-DXd without progression (Figure 1C). Treatment-related adverse events did not occur during treatment.

A gene panel test (FoundationOne® CDx, Foundation Medicine, USA) was performed, and genetic alterations were identified as follows: tumor mutational burden 18 Mut/Mb, ERBB2 amplification (copy number, 3.71), MYC amplification, BCL2L1 amplification, CDH1 loss, EZH2 duplication, NSD3 amplification, and PARK2 deletion.

Table 1. Treatment history before the T-DXd rechallenge.

| Line | 1st | 2nd | 3rd | 4th | 5th | 6th |
|------|-----|-----|-----|-----|-----|-----|
| Regimen | SOX+Tmab | PTX+Ram | IRI | T-DXd | ICI-based | Nivo |
| Treatment period (months) | 12.9 | 5.1 | 5.3 | 6.9 | 6.9 | 2.1 |
| Best response | PR | PR | SD | PR | PR | PD |

ICI = immune checkpoint inhibitor; IRI = irinotecan; Nivo = nivolumab; PD = progressive disease; PR = partial response; PTX = paclitaxel; Ram = ramucirumab; SD = stable disease; SOX = S-1+oxaliplatin; T-DXd = trastuzumab deruxtecan; Tmab = trastuzumab.
Figure 1. Computed tomography scans. (A) Before the rechallenge with trastuzumab deruxtecan (T-DXd), wall thickening in the cardia of stomach was observed; the length of the stomach wall was 29.3 mm. (B) After 3 cycles of T-DXd, shrinkage of the primary tumor was observed; the length of the stomach wall was 16.0 mm. (C) After 7 cycles of T-DXd, shrinkage of the primary tumor was observed; the length of the stomach wall was 11.8 mm.

Figure 2. Upper gastrointestinal endoscopy. (A) Before rechallenge with trastuzumab deruxtecan (T-DXd), gastric wall thickening in the cardia of the stomach was observed. (B) After four cycles of T-DXd, shrinkage of the primary tumor was observed.
Table 2. Laboratory data on the administration of T-DXd.

| Tumor marker | Normal range |
|--------------|--------------|
| CEA          | 2.3 ng/mL    |
|             | <5.0         |
| CA19-9       | 42.2 U/mL    |
|             | <37.0        |
| CA125        | 61.0 U/mL    |
|             | <26.9        |

ALT – alanine aminotransferase; AST – aspartate aminotransferase; BUN – blood urea nitrogen; Ca – calcium; CA19-9 – carbohydrate antigen 19-9; CA125 – cancer antigen 125; CEA – carcinoembryonic antigen; CRP – C-reactive protein; K – potassium; LDH – lactate dehydrogenase; Na – sodium; T-DXd – trastuzumab deruxtecan.
Discussion

Herein, we have reported the first case of a dramatic response to T-DXd rechallenge in a patient with HER2-positive gastric cancer, with HER2 positivity being confirmed immediately before the rechallenge. This case suggested that re-biopsy immediately before the T-DXd rechallenge was important, and in the case of HER2 overexpression, T-DXd rechallenge was helpful.

Some previous reports have indicated the loss of HER2 positivity after initial trastuzumab-based chemotherapy; the T-ACT study, the most recent study in Japan, demonstrated that HER2 positivity is maintained at only 31% after trastuzumab-based chemotherapy [8,10,11]. This study also showed an association between trastuzumab-free intervals and the efficacy of trastuzumab beyond progression. The data suggest that HER2 is re-expressed during trastuzumab-free chemotherapy. Three possible mechanisms underlie HER2 loss: (1) clonal selection, (2) heterogeneity of HER2 expression, and (3) use of fixatives other than 10% neutral buffered formalin [11]. Whether the loss of HER2 positivity occurred after T-DXd challenge remains unclear. In our case, although the expression of HER2 became weak after T-DXd challenge, the overexpression of HER2 was maintained.

In the DESTINY-Gastric01 study, the overall response rate (ORR) for T-DXd in gastric and GEJ adenocarcinoma with HER2 overexpression was significantly higher than that with chemotherapy (51.3% vs 14.3%, P<0.001) [6]. Explanatory analysis of the DESTINY-Gastric01 study showed that the ORR for T-DXd in gastric and GEJ adenocarcinoma with low expression of HER2 is 26.3% (for IHC 2+/ISH-negative) or 9.5% (for IHC 1+) [12]. Another study demonstrated this efficacy, regardless of the time at which the HER2 status was tested (before trastuzumab vs after during trastuzumab) [13]. Furthermore, it included patients with ≥2 prior regimens, and a trastuzumab-free interval of several months was assumed. The HER2 status of almost all patients was considered positive, regardless of the time of biopsy in this study. As mentioned previously herein, the loss of HER2 occurred after trastuzumab treatment; therefore, confirmation of HER2 overexpression would be important to maximize the efficacy of T-DXd.

In gastric and GEJ adenocarcinoma, biopsies are generally difficult to perform for patients with recurrent cancer after resection of the primary tumor. Anti-epidermal growth factor receptor (EGFR) antibodies are effective for patients RAS-wild-type colorectal cancer (CRC) but are ineffective for those with RAS-mutant CRC. Anti-EGFR therapy for RAS wild-type CRC induces resistance through acquired genomic alterations, especially through RAS mutations. The acquired RAS mutations can be detected by measuring circulating tumor DNA (ctDNA), and patients without acquired RAS mutations might benefit from anti-EGFR antibody rechallenge. Acquired RAS mutations disappear with time after the withdrawal of anti-EGFR antibodies. By monitoring the RAS status using liquid biopsy, rechallenge with anti-EGFR antibodies can be considered for RAS wild-type tumors, assessed based on ctDNA. The CHRONOS trial showed the efficacy of ctDNA-driven rechallenge with anti-EGFR antibodies for CRC [14]. In gastric and GEJ adenocarcinomas, re-biopsy is not a standard procedure. This suggests that monitoring the HER2 status by biopsy from a primary tumor should be helpful for T-DXd rechallenge. Although liquid biopsy is easier to perform, including in re-testing, the DESTINY-Gastric01 study showed the efficacy of T-DXd regardless of the ERBB2 plasma copy number in ctDNA [13]. A predictive plasma marker that can be easily used to study gastric and GEJ adenocarcinoma treated with T-DXd should be investigated.

Recently, nivolumab and triluluridine/tipiracil have been approved for the treatment of gastric and GEJ adenocarcinoma. However, their response rate is only 4-11% [15-17], which is notably lower than that of T-DXd. The idea that the usefulness of T-DXd rechallenge can be determined by re-biopsy from the tumor and that the rechallenge would be meaningful if the tumor is HER2-positive could be of clinical importance.

Conclusions

We report the first case of response to T-DXd rechallenge in HER2-positive gastric and GEJ adenocarcinoma. Rechallenge with T-DXd could be a treatment strategy worth considering for HER2-positive gastric cancer for cases in which the initial T-DXd treatment was effective. Confirmation of HER2 overexpression immediately before T-DXd rechallenge would be important, and re-biopsy could be a helpful and appropriate procedure for HER2-positive gastric and GEJ adenocarcinoma before T-DXd rechallenge.

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Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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