Hematology/Oncology and Stem Cell Therapy

Volume 17 | Issue 1 Article 9

Fam-Trastuzumab Deruxtecan (Enhertu) Induced pyloric perforation in hormonal receptor positive/ HER2 low express metastatic breast cancer.

Taher AL-Tweigeri
Medical Oncology Section, Oncology Centre, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia, ttwegieri@kfshrc.edu.sa

Recommended Citation
AL-Tweigeri, Taher (2023) "Fam-Trastuzumab Deruxtecan (Enhertu) Induced pyloric perforation in hormonal receptor positive/ HER2 low express metastatic breast cancer.," *Hematology/Oncology and Stem Cell Therapy*: Vol. 17 : Iss. 1 , Article 9.
Available at: https://doi.org/10.56875/2589-0646.1105

REVIEW

Fam-Trastuzumab Deruxtecan (Enhertu) Induced Pyloric Perforation in Hormone Receptor-positive/ HER2-low Expresses Metastatic Breast Cancer

Taher AL-Tweigeri*

Medical Oncology Section, Oncology Centre, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia

Keywords: Advanced breast cancer, Hormone receptor positive Her2 low express1+, Antibody drug conjugate

Dear Editor

Antibody-drug conjugates have been revolutionary in improving personalized cancer therapies in recent years. Fam-trastuzumab deruxtecan (T-DXd) was approved in August 2022 by the Food and drug administration (FDA) for use in adult patients with hormone receptor-positive (HR+)/HER2-low metastatic breast cancer based on the results of the DESTINY04 phase III clinical trial. T-DXd-induced gastrointestinal perforation has not yet been addressed in the literature. The purpose of this article is to present a case-based review of a unique pyloric perforation with the use of T-DXd.

A 72-year-old post-menopausal woman with a known case of type II diabetes mellitus with mild non-proliferative retinopathy who presented with right breast mass proven invasive ductal carcinoma estrogen receptor-positive, HER-2-low express 1+, and complete baseline staging with no reported distant metastasis, had right modified mastectomy and axillary lymph node resection in April 2015, which turned to be pathological T2N1M0. At that time, the patient agreed to participate in the Rx-PONDER clinical trial. Based on an Oncotype DX recurrence score of 17, the patient was randomized to endocrine therapy of letrozole. She had letrozole from June 2015 until May 2016. Unfortunately, in May 2016, the patient presented with chest wall recurrence. Complete resection was performed, which revealed the same tumor biology. At this point, she switched to Exemestane (Aromasin). Radiotherapy was applied to the chest wall and completed in September 2016. A PETCT scan, performed in July 2019, revealed extensive metastatic disease involving the lungs, bones, liver, and soft tissues. At this point, the patient had a lung biopsy, which confirmed invasive ductal carcinoma grade 3, a strongly positive ER PR of 90%, and HER-2 remained HER2 low. The patient started on fulvestrant (Faslodex), Palbociclib (Ibrance), and denosumab (the treatment modality started in August 2019). The patient arrived from the USA to continue her follow-up at our institute. Unfortunately, in June 2021, PETCT revealed a definitive disease progression in the lungs, liver, and bones, with a significant increase in the tumor marker (CA15-3). The patient started on weekly paclitaxel and Gemcitabine, and completed eight cycles of restaging. A new liver biopsy showed further disease progression, IDC, Grad II, ER 80%, and PR negative HER2 low1+. IMPACT GENOMIC TESTING: three mutations, no copy number alteration, one structural variant detected, MSI reported as stable, and the MSI sensor was 0.52. Tumor mutation burden: estimated

Received 14 February 2023; revised 10 April 2023; accepted 1 March 2023.
Available online 20 July 2023

* Section of Medical Oncology, Oncology Center, King Faisal Specialist Hospital & Research Center, PO Box 3354, Riyadh 11211, Saudi Arabia.
Fax: +966114423941.
E-mail address: ttwegieri@kfshrc.edu.sa.

https://doi.org/10.56875/2589-0646.1105

as 2.5 mutations per megabase, and the following somatic alteration was detected (TP53, KMT2C, NTRK1, and RB1). At this point, the USA Oncologist recommended ten cycles of Liposomal Doxorubicin, which was completed with partial response. Unfortunately, this complication by cardiomyopathy was characterized by a low ejection fraction of 40% and a significant drop in Global longitudinal strain (GLS) of −12.9. The patient started on maximum anti-failure medication with close observation in the cardio-oncology clinic. Another PETCT scan showed further disease progression in soft tissues with the appearance of moderate pleural effusion. The clinic suggested starting a single agent Eribulin or transferring to palliative care. Despite all the risks, the DestinyBreast04 patient agreed to consider intravenous administration of T-DXd every three weeks. The patient completed eight cycles with no major toxicities, including stable cardiac status with no changes in ejection fraction and improvement in GLS.

Two weeks post-cycle, the patient presented to the emergency department with a sudden sharp epigastric pain radiating to the left shoulder with one episode of vomiting. The patient was stabilized and sent home, but called in for urgent admission the following day, based on radiological findings of free air under the diaphragm.

She was admitted urgently and managed conservatively with NPO, IV fluids, antibiotics, pain control, and serial abdominal examinations, and then started the proton pump inhibitor Esomeprazole. Surgical, anesthesia, and cardiology teams were contacted for possible surgical intervention. Her CBCD, hepatic, renal profiles, electrolytes, and INR were all within normal limits. On the abdominal X-ray, there was pneumoperitoneum in the left upper quadrant. The CT scan showed a gastric wall defect associated with free air foci and contrast extravasation at the pylorus compatible with pyloric perforation (Fig. 1). The echocardiogram revealed an ejection fraction of 40% and a GLS of −14.6%. The left ventricular systolic function was moderately reduced, the patient was kept under observation, and a follow-up CT scan with oral contrast showed no evidence of a definite sizeable oral contrast leak, stable air foci, and prominent inflammatory changes at the vicinity of the stomach compatible with perforation; therefore, the patient was discharged in a stable condition.

Treatment of advanced breast cancer has evolved significantly in recent years with the approval of new target agents. Fam Trastuzumab Deruxtecan (T-DXd) is an antibody-drug conjugate comprising a tetrapeptide-based cleavable linker and a topoisomerase1 inhibitor payload. It is a new addition to the class of therapies that target the human epidermal growth2 (HER2) receptors [1–3]. T-DXd was approved in August 2022 for adult patients with unresectable or metastatic hormone receptor-

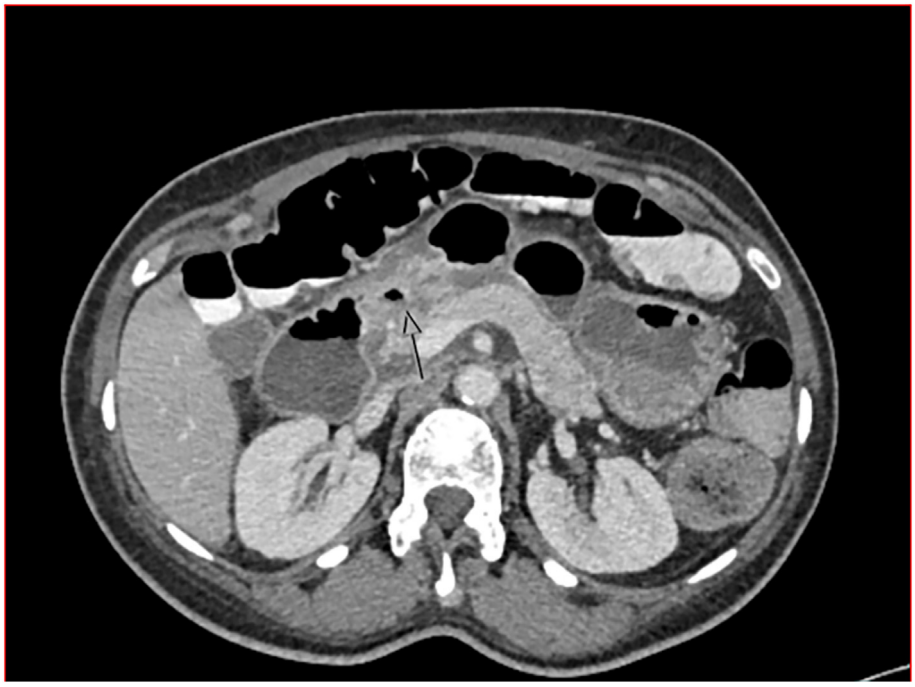

Fig. 1. A wall defect at the gastric pylorus associated with small volume contrast extravasation, trace free fluid, and few foci of intraperitoneal free air as well as surrounding fat stranding (marked with arrow), compatible with perforation.

positive (HR+)/HER2 low express (defined as an immunohistochemistry [IHC] score of 1+ or 2+ with negative in situ hybridization score) breast cancer who have received one or two prior lines of chemotherapies in a metastatic setting or have developed disease recurrence during, or within, six months of completing adjuvant setting [1]. The efficacy was based on DESTINY-BREAST04, a randomized phase III clinical trial that demonstrated a significant improvement in progression-free and overall survival [4].

Since T-DXd was recently approved and has a novel mechanism of action, a better understanding of adverse events (AEs) is needed to ensure patient benefits. The prescribing information recommended monitoring certain AEs based on clinical trial evidence; however, real-world clinical experience can bridge the gap between clinical research and practice [1]. According to the pooled results, the safety profile of T-DXd treatment was acceptable. The most common AEs were related to gastrointestinal and hematological toxicities. In all grades, nausea, vomiting, decreased appetite, fatigue, anemia, neutropenia, constipation, and diarrhea had rates of >30% [5]. In the phase 1 dose-escalating study, the safety, tolerability, and maximum tolerated dose recommended for the phase 2 study were examined. Three serious AEs have been reported: febrile neutropenia, intestinal perforation, and one patient had intestinal perforation that occurred on day 136, while our case occurred on day 168 [6] and reported cholangitis.

Modi et al. reported that fourteen patients (3.8%) in the T-DXd group and five (2.9%) in the physician's choice group had AEs associated with death. Those in the T-DXd group were due to: pneumonitis, ischemic colitis, disseminated intra-vascular coagulation, and sepsis [4].

Cardiac toxicities, unlike other HER2-targeted therapies, showed clinically significant cardiomyopathy associated with T-DXd [7], which was similar to our case, where the ejection fraction and GLS were unchanged during treatment.

The findings from the phase III DESTINY-BREAST04 study support the use of T-DXd in metastatic HER2 low 1+ and 2+ (IHC) breast cancer and should be considered as a new standard of care for patients who otherwise have limited options, such as our patients who failed most lines of therapies. T-Dxd has been increasingly used to treat both HER2 positive and HER2 low breast patients and will soon have promising potential to be used in the early stage of disease. To our knowledge, this is the first case of gastric perforation and the second to show that T-DXd can induce gastrointestinal perforation. Therefore, physicians should be alert to life-threatening AEs since their occurrence is unpredictable.

Conflicts of interest

Dr. Taher Al-Tweigeri has received speaking Honoraria from Roche, Novartis, and Lilly, received travel support from Novartis, and has served on an advisory committee for Lilly and Novartis.

References

[1] Bardia A, Harnden K, Mauro L, Pennisi A, Armitage M, Soliman H. Clinical practices and institutional protocols on prophylaxis, monitoring, and management of selected adverse events associated with trastuzumab deruxtecan. The Oncologist 2022 Aug;27(8):637–45.

[2] Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N, et al. DS-8201a, A Novel HER2-targeting ADC with a novel DNA Topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1Preclinical efficacy of DS-8201a, a novel HER2-targeting ADC. Clin Cancer Res 2016 Oct 15;22(20):5097–108.

[3] Rugo HS, Bianchini G, Cortes J, Henning JW, Untch M. Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer. ESMO open 2022 Aug 1;7(4):100553.

[4] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022 Jul 7;387(1):9–20.

[5] Xu H, Zhang H, Guo W, Zhong X, Sun J, Zhang T, et al. Safety and efficacy profile of Trastuzumab deruxtecan in solid cancer: pooled reanalysis based on clinical trials. BMC Cancer 2022 Dec;22(1):1–9.

[6] Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. Lancet Oncol 2017 Nov 1;18(11):1512–22.

[7] Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, Andre F, Iwata H, Ito Y, Tsurutani J. Updated results from DESTINY-breast01, a phase 2 trial of trastuzumab deruxtecan (T-DXd) in HER2 positive metastatic breast cancer. InSan Antonio Breast Cancer Symposium 2020 Dec. 8;81(4_Supplement):PD3–06.