Unexpected Cardiotoxicity in Patients With HER2-Mutant NSCLC Treated With Trastuzumab Deruxtecan: A Case Report

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ABSTRACT

Antibody-drug conjugates targeting receptor tyrosine-protein kinase erbB-2 (ERBB2, HER2) have emerged as promising targeted options for HER2-mutant NSCLC. Among antibody-drug conjugates targeting HER2, trastuzumab deruxtecan was found to have the most impressive efficacy and is a potential new standard of care. Drug-related interstitial lung disease remains a serious unpredictable identified risk for patients treated with trastuzumab deruxtecan, requiring careful monitoring and multidisciplinary management. We report the first two cases of drug-related cardiotoxicity with acute myocarditis that developed after the first trastuzumab deruxtecan cycle. Routine cardiovascular risk screening is advisable, with close collaboration between cardiology specialists and oncologists.

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Introduction

Human EGFR2 (HER2, ERBB2) mutations are found in approximately 1% to 4% of nonsquamous lung cancer cases.1,2 Today, NSCLC harboring HER2 alterations is considered a distinct subgroup of NSCLC with a driver molecular alteration. Targeted therapies against HER2 have substantially improved the prognosis of patients with breast and gastric cancers; however, they are yet to be approved in HER2-mutant NSCLC.3 Antibody-drug conjugates (ADCs) are novel antitumor agents that combine the particular binding capacities of monoclonal antibodies with the cytotoxic activity of chemotherapy to specifically target and damage tumor cells.3 Trastuzumab deruxtecan (T-DXd or DS-8201a) is an emerging

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HER2-targeting ADC composed of trastuzumab, an enzymatically cleavable peptide linker, and a novel topoisomerase I inhibitor called MAAA-1181. Its mechanism of action differs from other ADCs because it binds to topoisomerase I-DNA complexes inducing DNA double-strand breaks and apoptosis.4

Results from the multicenter, single-arm, phase 2 trial DESTINY-Lung01, evaluating the efficacy of trastuzumab deruxtecan in refractory NSCLC harboring HER2 molecular alterations, were recently published. Unprecedented efficacy data were reported, notably in the HER2-mutant cohort, with an overall response rate of 55% (95% confidence interval [CI]: 44%–65%) and median duration of response of 9.3 months (95% CI: 5.7–14.7). Median progression-free survival and overall survival were 8.2 months (95% CI: 6.0–11.9) and 17.8 months (95% CI: 13.8–22.1), respectively.5,6

The most common adverse events (AEs) associated with ADCs are gastrointestinal and hematologic of any grade. In the DESTINY-Lung01 trial, 26% of patients in the HER2-mutant cohort presented drug-related interstitial lung disease, which resulted in death in two cases.6 So far, no other serious AEs have been reported with trastuzumab deruxtecan. Here, we present two cases of cardiac toxicity in patients with HER2-mutant NSCLC treated with trastuzumab deruxtecan.

Case Presentations

Case 1

A 69-year-old nonsmoker woman was diagnosed in December 2019 with having a lung adenocarcinoma with bilateral lung metastases harboring an HER2 exon 20 insertion (p.Tyr772_Ala775Dup) detected by next-generation sequencing. She had type 2 diabetes, hypertension, high cholesterol, and obesity grade I. She received first-line treatment with four cycles of carboplatin (area under the curve [AUC]5), pemetrexed (500 mg/m²), and pembrolizumab (200 mg), every 3 weeks achieving a partial response, followed then by maintenance with pemetrexed and pembrolizumab until early August 2021 (total of 4 + 20 cycles). Stereotaxic lung radiotherapy was delivered to the left lung lobe in November 2020 (no further information available). Result of a computed tomography (CT) scan in August 2021 revealed progression in the lung, and the patient was included in the phase 2 randomized DESTINY-Lung02 study with trastuzumab deruxtecan as a second-line therapy. After screening, including a cardiac evaluation revealing no morphologic or functional alterations, treatment was started at blinded dose 6.4 mg/kg or 5.4 mg/kg every 3 weeks in October 2021.

Twenty-one days after the first trastuzumab deruxtecan infusion (November 2021), elevated troponin I levels were reported (1910 pg/mL) without symptoms, during a per-protocol visit. The patient was referred to the cardiology department where an electrocardiogram (ECG) result was normal and no repercussions on the left ventricular ejection fraction (LVEF) were observed in a transthoracic echocardiography (TTE). A coronary angiography was performed as the patient was considered to be high-risk; however, no significant lesions were identified. Cardiac magnetic resonance imaging (MRI) results revealed signs of acute myocarditis according to Lake Louise Criteria (LLC), with apical/subepicardial late gadolinium enhancement (LGE) associated with local increase of native T1 (1200 msec; LLC-T1 > 1000 msec; normal 950–1000 msec) and T2 (72 msec; LLC-T2 > 55.9 msec; normal 40–50 msec) (Fig. 1).7,8 As myocarditis has never been reported with trastuzumab deruxtecan, a right ventricular endomyocardial biopsy was performed, which found no lymphocytic infiltrates and any other alteration. Serology and autoimmunity parameters were negative, with no epidemiologic context or symptoms of viral infection.

Treatment with trastuzumab deruxtecan was discontinued after the first cycle owing to this abnormality. The patient presented spontaneous favorable clinical evolution and her troponin I levels rapidly lowered, allowing hospital discharge 4 days after the event.

Figure 1. Case 1. Myocarditis as revealed by cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging of patient 1 revealing subepicardial late gadolinium enhancement (arrow) of the inferior lateral apical wall, suggestive of myocarditis, found on the short-axis view (left panel), and the three chambers on the long-axis view (right panel). LA, left atrium; LV, left ventricle; RV, right ventricle.
A cardiac evaluation in January 2022 revealed complete normalization of troponin I with normal and stable ECG and TTE parameters. After disease progression in February 2022, the patient started third-line therapy with weekly paclitaxel 80 mg/m² and trastuzumab 6 mg/kg every 3 weeks, with no significant toxicities and stable cardiac function at the last follow-up in June 2022.

**Case 2**

A 57-year-old nonsmoker man was diagnosed in August 2020 with having an extensive lymphangitic lung adenocarcinoma carrying a duplication in HER2 exon 20 (p.Y772_A775dup). As other medical conditions, he presented a medically controlled hypertension, pulmonary embolism, and a deep vein thrombosis of the right upper extremity treated with a new oral anticoagulant.

He received first-line therapy with cisplatin 75 mg/m² and pemetrexed 500 mg/m² every 3 weeks achieving a partial response after three cycles and continued with maintenance pemetrexed monotherapy. Progression in the lung was documented by CT scan in May 2021, and second-line treatment with nivolumab 2 mg/kg every 2 weeks was started in June 2021. Nevertheless, new bone and infra-diaphragmatic lymph node lesions were detected 4 months after, in October 2021.

The patient was prescreened for inclusion in the phase 2 DESTINY-Lung02 study. Baseline troponin I level was 141 pg/mL (upper limit: 45 pg/mL), related to a mild pericardial effusion identified by TTE during a recent visit with the patient’s cardiologist. The case was discussed with cardiology experts, who concluded that tumoral pericardial infiltration was more likely than an immune-related cardiac complication because nivolumab was discontinued in September 2021, after five injections. Thus, in the absence of any contraindication, treatment with trastuzumab deruxtecan was initiated in November 2021, after 2 months of immunotherapy discontinuation.

Increased troponin I level (to 1368 pg/mL) was reported during a per-protocol visit 7 days after the treatment initiation. The patient reported recent recurrent chest pain episodes starting 48 hours after trastuzumab deruxtecan administration. Repolarization alterations with T biphasic waves in V3 to V6 and DII to DIII/avF found at baseline were present in a repeat ECG result. TTE found a moderate to severe pericardial effusion with no clinical signs of hemodynamic compression. A cardiac MRI confirmed a circumferential pericardial effusion of 35 mm in width; there was no evidence of LGE, and mild local elevation of T2 and native T1 was noted on the basal anteroseptal wall (T2 = 62 msec; T1 = 1050 msec), suggestive of possible early stage myocarditis (Fig. 2). The patient was admitted to the cardiac intensive care unit for pericardial drainage (650 mL). Cytologic analyses found evidence of tumoral cells. Serology and autoimmunity parameters were negative. A coronary angiography did not find any endovascular lesion. Endomyocardial biopsy was not performed after recent pericardial drainage. A control cardiac MRI performed 10 days after revealed no recurrence of pericardial effusion and appearance of a mid-septal LGE lesion suggestive of myocarditis. As in case 1, no specific treatment was administered, and after a slow and progressive decrease in troponin I levels and no evidence of cardiac complications, the patient was discharged (13 d after the initial event). No further treatment with trastuzumab deruxtecan was administered.

Result of a CT scan at the end of December 2021 revealed stable disease per Response Evaluation Criteria in Solid Tumors version 1.1. In early February 2022, the patient started a new line of treatment with weekly carboplatin area under the curve 2 and paclitaxel 80 mg/m² after a positron emission tomography-CT scan revealing lung and diffuse bone progression. An echocardiography in March 2022 revealed a mild pericardial effusion with a conserved LVEF (Fig. 2A). A subsequent 3-month control cardiac MRI revealed a more obvious septal mediomural myocarditis scar with normal T1 and T2 values (Fig. 2B). At the last follow-up (July 2022), the patient was well and still receiving the same chemotherapy regimen.

**Discussion**

New therapeutic opportunities are being explored with the emergence of HER2-targeted therapies in HER2-driven advanced NSCLC. Novel selective HER2 tyrosine kinase inhibitors such as poziotinib and pyrotinib were found to have promising activity in HER2-mutant previously treated NSCLC, with overall response rates up to 38% and 44%, respectively. Nevertheless, the most encouraging data come from phase 2 studies evaluating the ADCs ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan in patients with HER2-mutant NSCLC, with response rates of 50% and 55%, respectively. In August 2022, the Food and Drug Administration granted accelerated approval to trastuzumab deruxtecan in refractory HER2-mutant NSCLC.

The phase 2 DESTINY-Lung02 (NCT04644237) was designed to evaluate the safety and efficacy of trastuzumab deruxtecan in patients with HER2-mutated metastatic NSCLC with disease recurrence or progression during or after at least one platinum-based...
chemotherapy regimen. To date, no treatment-related cardiac AEs have been declared with trastuzumab deruxtecan in lung cancer. Among the phase 2 studies evaluating ado-trastuzumab emtansine, only Peters et al.\(^9\) reported two cases of grades 1 to 2 cardiac dysfunction in patients with HER2-overexpressing NSCLC, without specifying further.

Cardiotoxicity with anti-HER2 tyrosine kinase inhibitors in lung cancer has been objectivated, although at low rates, with pyrotinib (grade 3 hypertension and prolonged QTc, both in 1.7% of cases) and with tarloxotinib (all-grade and grade 3 prolonged QTc observed in 61% and 39% of cases, respectively).\(^3\) As expected, in studies evaluating the combination of the monoclonal antibody trastuzumab with chemotherapy in HER2-positive NSCLC, 6% to 7% of patients in the combination arm presented decreased LVEF which caused treatment discontinuation in one patient treated with cisplatin-gemcitabine plus trastuzumab.\(^3\)

In the phase 2 DESTINY-Breast01 trial evaluating trastuzumab deruxtecan in metastatic HER2-positive breast cancer after prior ado-trastuzumab emtansine, grade 3 or higher cardiotoxicity occurred in only 1.6% of patients (two prolonged QT intervals and one case of decreased LVEF), whereas interstitial lung disease was the main safety signal of concern leading four deaths (2.2%).\(^10\) LVEF decline was also observed with ado-trastuzumab emtansine, at a comparable or even lower rate (<2%) than with other treatments including trastuzumab, lapatinib, or chemotherapy.\(^11\)-\(^15\) In the gastric cancer setting, any case of decrease in LVEF or heart failure was described in DESTINY-Gastric01; results in the phase 2 are awaiting.\(^16\)

Thus, to date, anti-HER2-related cardiotoxicity has been only reported in the form of electric or functional alterations. Only Wadhwa et al.\(^17\) found that during a 6-month-follow-up, 34 of 36 patients with breast cancer with trastuzumab-induced cardiomyopathy had...

**Figure 2.** Case 2. Transthoracic echocardiography and cardiac MRI revealing a large pericardial effusion and late appearance of myocarditis. (A) Transthoracic echocardiography, four-chamber view at baseline, 8 days after the first trastuzumab deruxtecan administration, revealing a severe circumferential pericardial effusion (*), inducing septal flattening. (B) Cardiac MRI: short-axis views revealing delayed enhanced images 10 minutes after gadolinium administration at baseline (left panel), 7 days after pericardial drainage (middle panel), and at 3 months (right panel). The initial cardiac MRI (left panel) confirmed a severe circumferential pericardial effusion without any obvious sign of myopericarditis (*), as revealed by the absence of pericardial and myocardial LGE. One week later (middle panel), after pericardial effusion was removed, a control cardiac MRI revealed intramural septal LGE (arrow) suggestive of myocarditis, confirmed at the 3-month cardiac MRI control (right panel). Pericardial enhancement found at the second cardiac MRI is probably reactional to pericardial drainage. LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; MRI, magnetic resonance imaging; RA, right atrium; RV, right ventricle.
subepicardial linear delayed enhancement of the lateral wall of the left ventricle on cardiac MRI, suggesting trastuzumab-induced myocarditis.

Our two patients both presented acute myocarditis, developed early at 7 and 21 days after initiating the treatment. Both presented with cardiovascular risk factors, which were more evident for the first case (Fig. 3). The second patient presented a pericardial effusion at baseline, and although the first and early cardiac MRI results were not consistent with inflammatory myocarditis, the large and rapid elevation of troponin I level and the appearance of chest pain 48 hours after trastuzumab deruxtecan initiation suggest the coexistence of two different entities, as revealed by imaging findings, with acute myocarditis induced by trastuzumab deruxtecan. Cardiac MRI parameters qualifying for myocarditis were initially incomplete, occurring slightly later, as found in patients with immunotherapy-induced myocarditis.18

Interestingly, both two cases were previously treated with immune checkpoint inhibitors before trastuzumab deruxtecan administration. Immune checkpoint inhibitor can induce acute myocarditis, and they could be considered one of the risk factors for cardiac toxicity development. The phase 2 study with trastuzumab emtansine plus atezolizumab in HER2-positive refractory breast cancer did not report any increase in cardiac toxicity19; the phase 1b study combining trastuzumab deruxtecan and pembrolizumab in HER2-positive refractory breast and lung cancers (NCT04042701), still ongoing, will probably add some relevant information in the near future.

In preclinical models focused in breast cancer, pembrolizumab plus trastuzumab lead to strong cardiac proinflammatory effects mediated by overexpression of NF-kB and leukotriene B4–related pathways20; and although this combination therapy was not associated with an increase in cardiac toxicity in breast cancer, four cases of decreased LEVF were described in the field of esophageal and gastric cancers.20,21 If radiotherapy in the upper left lobe in case 1 may have also contributed to myocarditis development remains an open and interesting question.

The NRG1 signaling axis is a critical component of the stress response of the heart. Neuregulin is secreted by the coronary endothelial cells, required for normal cardiac growth and maintenance, with a putative role in myofilament architecture, cell survival, glucose metabolism, contractility, angiogenesis, and conduction system.22,23

NRG1 binds to the HER2-ERBB4 receptor dimers on the cardiac myocyte plasma membrane, activating downstream effectors critical for protection against oxidative stress and induced cell death, including the PI3K-AKT, MAPK, and JAK/STAT3 pathways. Therefore, trastuzumab blocks NRG1 function, promoting the damaging effects of oxidative stress, leading to DNA breakage and mitochondrial apoptosis.22,23 In cardiac myocyte-specific ERBB2- and ERBB4-conditioned knockout mice, cardiomyopathy developed by 8 to 12 weeks of life.24

Consensus documents and guidelines on cardiotoxicity with cancer therapy generally agree that before starting any potentially cardiotoxic therapy, all patients should...
undergo a baseline assessment of cardiac function, including a complete screening of any potential cardiovascular diseases and risk factors, the realization of an ECG, an TTE plus baseline troponin measurement. Imaging by cardiac MRI is recommended as an alternative to TTE once LVEF falls, or when poor image quality prevents accurate measurements. In breast cancer, elevation in troponin I level predicts LVEF reduction and cardiac AEs in patients treated with trastuzumab, particularly in those who have previously received anthracyclines, and measurements should be taken before and/or 24 hours after each cycle of cancer therapy. HER2 mutations are a targetable driver for HER2-directed therapies in NSCLC. Strategies for preventing, monitoring, and detecting cardiac AEs associated with anti-HER2 agents are needed. Although preexisting risk factors can identify many high-risk patients, a significant number present no known predisposing factors. Additional criteria, including imaging data and blood-based biomarkers such as troponin, may be required to improve the accuracy of future risk models. Given the present two consecutive cases of cardiotoxicity with trastuzumab deruxtecan, we strongly encourage to systematically monitor troponin I levels before each injection of anti-HER2 ADCs.

So far, any specific protocol exists for the management of cardiac toxicity related to trastuzumab deruxtecan and other anti-HER2 ADCs; however, most recent guidelines on cardio-oncology recommend to start cardioprotective therapy with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and beta-blockers when cardiac dysfunction related to HER2-targeted therapy occurs.

The mechanisms of action of ADCs remain poorly understood and require additional studies to elucidate unanswered speculations about these molecules and to better define the target population and mechanisms of toxicity, especially pulmonary and cardiac, as in our two patients.

Conclusions

In conclusion, to our knowledge, we report here the first two cases of trastuzumab deruxtecan-induced cardiotoxicity in the form of acute myocarditis, appearing early after the first treatment injection. These two cases reinforce the importance of routine troponin monitoring from initiation of trastuzumab deruxtecan and the role of cardiac MRI to depict myocarditis in these patients and suggest that repeat cardiac MRI may be useful in the event of an initial “negative” outcome. Further investigation into screening, understanding, and management is required to limit cardiotoxicity related to trastuzumab deruxtecan.

CRediT Authorship Contribution Statement

Mariona Riudavets: Conceptualization, Data curation, Writing—original draft.
Arshid Azarine, Sondes Smaali, Young-Wouk Kim: Data curation, Validation, Writing—review and editing.
Vincent Thomas de Montpréville, Alina Miruna Grecea, Charles Naltet, Anna Gazzah: Validation, Writing—review and editing.
David Planchard: Project administration, Conceptualization, Data curation, Supervision, Validation, Writing—review and editing.

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