CASE REPORT

Successful Rechallenge of Trastuzumab Deruxtecan After Drug-Induced Interstitial Lung Disease in a NSCLC With *HER2* Mutation: A Case Report

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ABSTRACT

Trastuzumab deruxtecan, an antibody-drug conjugate targetingHER2-expressing tumor cells, was found to have promising results in treatment-refractory, metastatic NSCLC harboring *HER2* mutations. Nevertheless, drug-induced interstitial lung disease (ILD)/pneumonitis is a concern that limits treatment response in this subset of patients. For grade 2 or more ILD/pneumonitis, permanent discontinuation is warranted with vigorous treatment with high-dose steroid. We report a case of successful rechallenge of trastuzumab deruxtecan after recovery of grade 3 ILD/pneumonitis in treatment-refractory NSCLC harboring *ERBB2* Y772-A775dup.

Keywords: Trastuzumab deruxtecan; Interstitial lung disease; ERBB2 Y772-A775; Non–small cell lung cancer; Case report

Introduction

HER2 mutation accounts for 2% to 4% of non-squamous NSCLC.[1] Recently, trastuzumab deruxtecan, an ADC targeting *HER2* mutation, received the U.S. Food and Drug Administration accelerated approval for *HER2*-mutant NSCLC. In Destiny lung-01 trial, trastuzumab deruxtecan at 6.4 mg/kg every 3 weeks was found to have durable antitumor activity with an overall response rate of 55%, median progression-free survival of 8.2 months (95% confidence interval [CI]: 6.0–11.9), and overall survival of 17.8 months (95% CI: 13.8–22.1).[2] Nevertheless, grade 3 or more adjudicated interstitial lung disease (ILD) accounted for 6.6% and was fatal in two patients. To access the benefit-risk profile trastuzumab deruxtecan, the phase 2 Destiny lung-02 trial was conducted to assess trastuzumab deruxtecan at 5.4 or 6.4 mg/kg every 3 weeks.[3,4] Both doses had clinically meaningful response with an overall response rate of 49% and 56% for 5.4 and 6.4 mg/kg, respectively. Trastuzumab deruxtecan at 5.4 mg/kg had favorable safety profile than 6.4 mg/kg with lower incidence of adjudicated ILD (12.9% versus 28%).

According to recommended guideline of ILD/pneumonitis management for trastuzumab deruxtecan, permanent discontinuation of the drug is recommended even at grade 2 as per Common Terminology Criteria for Adverse Events version 5.0.[5] For grades 3 and 4 ILD/pneumonitis, trastuzumab deruxtecan must be

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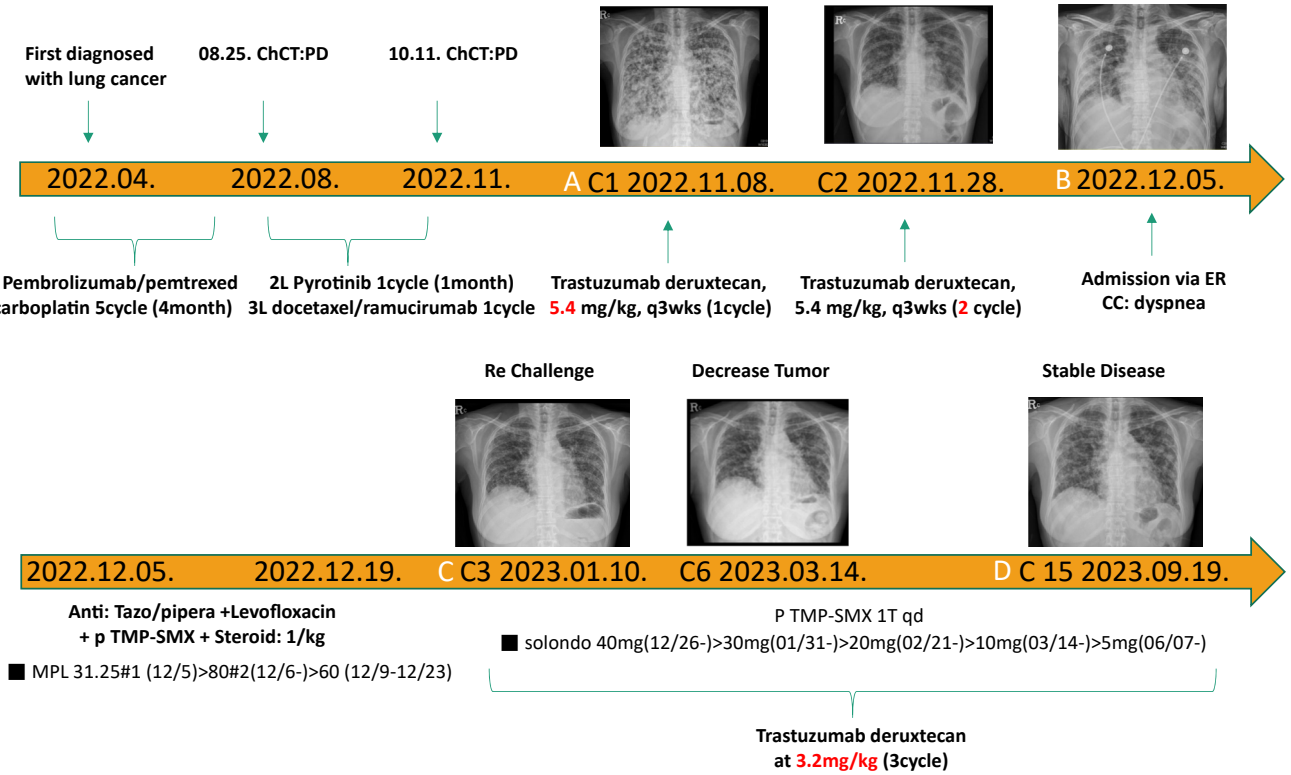

Figure 1. Timeline for trastuzumab deruxtecan rechallenge for pneumonitis.

permanently discontinued and hospitalization is required with high dose of intravenous corticosteroid. Here, we describe a case of a patient diagnosed with having *HER2*-mutant NSCLC with successful rechallenge of trastuzumab deruxtecan after recovering from grade 3 ILD.

Case Presentation

A 50-year-old woman without any past medical history was diagnosed with having lung adenocarcinoma with metastasis to bilateral lung in in April 2022. Molecular testing results for *EGFR*, *ALK*, and *ROS1* were negative. Next-generation sequencing of tumor tissue revealed *ERBB2* Y772-A775dup mutation.

The patient was initially treated with 5 cycles of pembrolizumab with pemetrexed and carboplatin but had disease progression with aggravation of hematolymphangitic metastasis of the lung. After progression, she was referred to Yonsei Cancer Center and was treated with pyrotinib, a novel, irreversible pan HER2 tyrosine kinase inhibitor (NCT04447118). Nevertheless, the patient relapsed after 1 month with aggravation of lung metastasis. After failure with systemic treatment with standard chemoimmunotherapy and HER2 tyrosine kinase inhibitor, the patient was to receive trastuzumab deruxtecan. Although U.S. Food and Drug Administration approved, the drug was not available at our institution or elsewhere, owing to the reimbursement issues in South Korea. At this time, patients with *HER2*-mutant NSCLC were not actively treated with trastuzumab deruxtecan and were treated with cytotoxic chemotherapy or enrolled to clinical trials for HER2 investigational agents. Despite the financial toxicity, the patient agreed to receive treatment with trastuzumab deruxtecan. In the meantime, the patient was treated with one cycle of docetaxel and ramucirumab (Fig. 1).

Subsequently, she was treated with trastuzumab deruxtecan given at 5.4 mg/kg every 3 weeks (Fig. 2*A*). The chest radiograph after 21 days revealed tumor shrinkage in bilateral lung metastasis. Nevertheless, the patient complained of chest discomfort and dyspnea after receiving two cycles of trastuzumab deruxtecan and visited the emergency room (Fig. 2*B*). Chest computed tomography revealed ILD/pneumonitis with pneumonia on both lungs. The patient was immediately treated with intravenous corticosteroids (1 mg/kg) and antibiotics including piperacillin/tazobactam and levofloxacin, in addition to trimethoprim sulfamethoxazole for prophylaxis of pneumocystis pneumonia. During the treatment, the patient was given high-flow nasal cannula, and intravenous corticosteroids (1 mg/kg) were maintained during this time. After 2 weeks, the patient had improvement, and high-flow nasal cannula was discontinued. The patient was discharged with 40 mg of

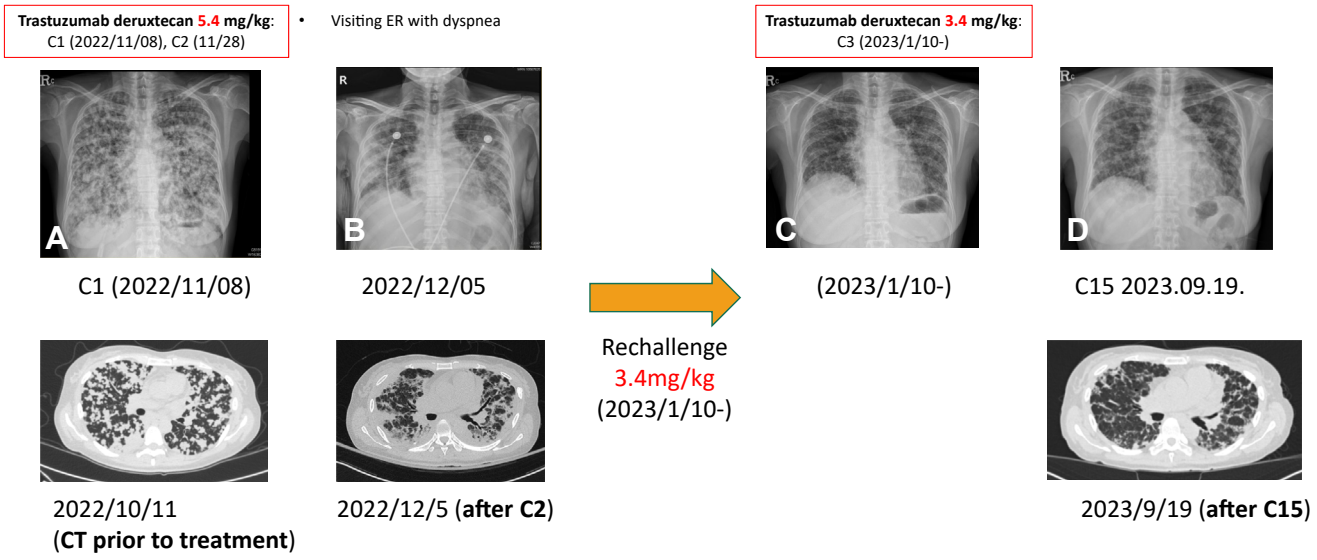

Figure 2. (*A*) Chest CT before treatment. (*B*) Chest CT after 2 cycles of trastuzumab deruxtecan, pneumonia with pneumonitis when visiting the ED. (*C*) Chest CT before trastuzumab deruxtecan rechallenge. (*D*) Chest CT after trastuzumab deruxtecan 3.4 mg/kg for pneumonitis. CT, computed tomography; ER, emergency room.

prednisolone and oral antibiotics. She revisited the outpatient clinic after 1 week and did not have any symptoms of dyspnea or chest discomfort and did not require oxygen support. Chest radiograph did not reveal signs of ILD/pneumonitis or pneumonia. Prednisolone was maintained at 40 mg after 3 more weeks, tapered to 30 mg for 4 weeks, 20 mg in the course of 3 weeks, and 10 mg for 12 weeks before maintaining prednisolone of 5 mg during treatment with trastuzumab deruxtecan.

After ILD/pneumonitis was resolved to grade 1, we discussed the next treatment option with the patient. Before consulting with the patient and her caregivers, three medical oncologists specializing in thoracic oncology at our center discussed the future potential options for the patient. She was no longer eligible for other clinical trials owing to the history of grade 3 pneumonitis/ILD. The first option was to permanently discontinue trastuzumab deruxtecan and receive standard chemotherapy. The second option was to continue trastuzumab deruxtecan at dose reduction while maintaining low dose of prednisolone. Earlier, the patient had already purchased trastuzumab deruxtecan for the next two cycles because the drug was not readily available in South Korea. The patient and caregivers were meticulously consulted with both options and the risk and benefit that followed. They chose to continue with trastuzumab and was rechallenged with dose reduction of 3.2 mg/kg every 3 weeks while maintaining prednisolone of 40 mg (Fig. 2*C*). As of September 23, 2023, the patient was treated with 15 cycles and is maintaining a partial response at 10 months without any incidence of ILD aggravation (Fig. 2*D*).

Discussion

Our case not only highlights the aggressive treatment of ILD/pneumonitis needed for patient treated with trastuzumab deruxtecan but also addresses the scrutiny for monitoring and diagnosing ILD/pneumonitis during treatment. Because most of the patients are treated in the outpatient clinic, proactive patient monitoring is strongly recommended.[1] Asking patients about their symptoms of each visit with assessment of oxygen saturation with pulse oximetry should be accompanied with routine chest radiograph and laboratory tests every 3 weeks.

ILD/pneumonitis resulting from immunotherapy is distinct from that of trastuzumab deruxtecan in clinical features. For ILD/pneumonitis owing to immunotherapy, rechallenge is encouraged for initial grade 2 on resolution to grade 1 and considered for permanent discontinuation for grade 3 ILD.[6] Although the incidence of adjudicated ILD is lower for the recommended dose of trastuzumab deruxtecan at 5.4 mg/kg compared with 6.4mg/kg every 3 weeks,[3,4] active surveillance for ILD/pneumonitis is critical during the maintenance of trastuzumab deruxtecan. Although permanent discontinuation of trastuzumab deruxtecan is recommended for grade 2 or higher ILD/pneumonitis,[1,5] the next treatment options for these patients remain limited to cytotoxic chemotherapy. The patients who have recovered with ILD/pneumonitis are no longer eligible for other clinical trials including novel HER2 agents owing to the history of ILD/pneumonitis. Although following the guideline for management of ILD/pneumonitis for trastuzumab

deruxtecan should be the standard practice, risk stratification and rechallenge should be considered for patients experiencing ILD/pneumonitis in the future. Our case was an exception to the standard practice and revealed that trastuzumab deruxtecan at 3.2 mg/kg can be successfully rechallenged even for grade 3 ILD/pneumonitis with the maintenance of low-dose steroid. Nevertheless, our case should not be generalized for all grade 3 pneumonitis. Instead, prospective studies on rechallenging trastuzumab deruxtecan after ILD/pneumonitis should be considered because rechallenging with immunotherapy in grade 2 is strongly advised.[7]

Conclusions

This case revealed that trastuzumab deruxtecan can be successfully rechallenged after resolution of grade 3 ILD/pneumonitis. Although this approach should be dealt with caution, it could be an option for patients with *HER2*-mutant NSCLC who have no subsequent therapeutic option. Meticulous monitoring of ILD aggravation while maintaining low-dose steroid during treatment is the key to successful rechallenge of trastuzumab deruxtecan.

CRediT Authorship Contribution Statement

Sangho Nam: Data curation, Writing—Original draft preparation, Conceptualization.

Jii Bum Lee: Writing—Reviewing and Editing, Methodology.

Sun Min Lim: Visualization, Software, Validation, Investigation.

Byoung Chul Cho: Supervision.

Disclosure

Dr. Lim reports receiving grants from Yuhan, Beigene, Boehringer Ingelheim, BridgeBio Therapeutics, Roche, GlaxoSmithKline, Jiangsu Hengrui, AstraZeneca, Lily, Takeda, Daiichi Sankyo, and J Ints Bio. Dr. Lee reports receiving research grants from Yuhan. Dr. Nam declare no conflict of interest.

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The patient involved in this case report gave her informed consent authorizing the use and disclosure of her health information.

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