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Clinical Perspectives on Drug-Induced Lung Injury Associated with Trastuzumab Deruxtecan: Real-World Evidence and Implications

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Abstract

Introduction: Trastuzumab deruxtecan (T-DXd) is used to treat human epidermal growth factor receptor 2-positive breast cancer, non-small cell lung cancer, and gastric cancer, with reports of favorable treatment outcomes. However, drug-induced lung injury associated with trastuzumab deruxtecan (T-DXd) therapy presents a significant challenge, with its incidence and clinical progression remaining poorly characterized in real-world settings. **Methods:** We enrolled 16 patients at Tokyo Medical University Hachioji Medical Center, Japan, between April 2020 and December 2024 who were suspected of drug-induced lung injury arising from T-DXd therapy. We categorized members of our patient cohort on the basis of the presence or absence of drug-induced lung injury and provided a detailed report. **Results:** Four out of 16 patients developed drug-induced lung injury within a median time period of 10.32 months (95% Confidence Interval: 9.26-NA). There was no difference in the clinical background between patients with and without drug-induced lung injury. Two patients exhibited the organizing pneumonia pattern, while two displayed the diffuse alveolar damage (DAD) pattern. One patient succumbed to the condition. **Conclusion:** It is difficult to predict the onset of drug-induced lung injury due to T-DXd, and the prognosis is poor in drug-induced lung injury that presents the DAD pattern.

Keywords

Trastuzumab Deruxtecan, Human Epidermal Growth Factor Receptor 2, Drug-Induced Lung Injury, Interstitial Lung Disease, Breast Cancer

1. Introduction

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate comprising an anti-human epidermal growth factor receptor 2 (HER2) humanized monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload [1]. The linker is designed to remain stable in plasma and selectively cleaved by cathepsins, which are upregulated in tumor cells. The cytotoxic payload, with a drug-to-antibody ratio of approximately 8:1, exhibits membrane permeability, potentially inducing a bystander effect by impacting neighboring cells irrespective of HER2 expression. Furthermore, its short half-life mitigates off-target effects, enhancing its precision and safety profile [2].

T-DXd is used as a treatment for HER2-positive breast cancer, non-small cell lung cancer, and gastric cancer, with reports of favorable treatment outcomes [3]-[7]. Interstitial lung disease (ILD), a notable adverse event linked to T-DXd therapy, has been frequently reported. The incidence of T-DXd-induced lung injury during breast cancer treatment is estimated to range between 10% and 15% [5]-[9]. Most cases are observed within the first 12 months of therapy, with a median onset time of 5.4 months. Notably, this period is shortened to 3.2 months for grade 5 events [9]. The pooled analysis identified several potential risk factors for T-DXd-induced lung injury, including a baseline peripheral oxygen saturation (SpO_2) of <95%, a T-DXd dose exceeding 6.4 mg/kg, a dosing frequency of q3w, a disease duration of over four years since the initial diagnosis, renal dysfunction, an age of <65 years, and baseline or prior lung comorbidities [9]. Nonetheless, the frequency and severity of lung injuries induced by trastuzumab deruxtecan (T-DXd) in real-world settings, along with their clinical progression, remain poorly characterized. Drug-induced lung injury can, in certain cases, result in fatal outcomes. Even when non-fatal, it may lead to a deterioration in the patients' overall health status, negatively affecting their prognosis. Consequently, it is crucial to understand the incidence of drug-induced lung injury and develop optimized management strategies to improve patient outcomes.

The purpose of this study was to determine the frequency and severity of T-DXd-induced lung injury in real-world settings and to report in detail the clinical course as a case series.

2. Materials and Methods

2.1. Patients and Study Design

This study included patients suspected of having T-DXd-induced lung injury who received treatment at Tokyo Medical University Hachioji Medical Center, Japan, between April 2020 and August 2024. Clinical data for each patient were retrieved from their medical records. All patients treated with T-DXd were confirmed to have no pre-existing pneumonia, including interstitial lung disease (ILD). Consequently, the newly observed ILD on chest computed tomography

(CT) was diagnosed as T-DXd-induced lung injury. High-resolution CT images were analysed by two respiratory physicians, who determined and classified the imaging patterns. The enrolled patients were divided into two groups: those diagnosed with T-DXd-induced lung injury and those without. The clinical characteristics of patients in both groups were retrospectively compared. Additionally, detailed case reports were compiled for patients diagnosed with T-DXd-induced lung injury. Patient survival was monitored until December 2024. The Ethics Committee of Tokyo Medical University approved this retrospective study protocol (Ethical Approval Number: T2024-0048) and waived the requirement for informed consent. However, we provided study participants the opportunity to refuse participation in this study using the opt-out method. All study methods were conducted in accordance with relevant guidelines and regulations.

2.2. Data Collection

We investigated the following patient characteristics: sex, age, estimated glomerular filtration rate (eGFR), SpO_2, T-DXd doses, the number of lines of treatment, number of courses of treatment, duration of T-DXd administration, percentage of breast cancer, and lung comorbidities, such as chronic obstructive pulmonary disease and interstitial lung disease. Patient age, eGFR value, SpO_2 percentage, and type of lung comorbidity were recorded at the start of T-DXd treatment.

2.3. Statistical Analysis

All values were expressed as medians and interquartile ranges. Fisher's exact test and the Mann-Whitney U test were used to compare baseline patient characteristics. The time of onset of T-DXd-induced lung injury was assessed using the Kaplan-Meier curve. A p-value of less than 0.05 was set as the threshold for statistical significance. Statistical analyses were performed using EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results

3.1. Patients' Characteristics

Between December 2020 and December 2024, a total of 16 patients underwent treatment with T-DXd. The median age of the patients was 61.5 (53 - 86) years; 81.3% were women, 87.5% had been diagnosed with breast cancer, and 12.5% with stomach cancer. Four out of 16 patients developed T-DXd-induced lung injury. No significant differences were observed in the characteristics of patients between the two groups (Table 1).

3.2. Drug-Induced Lung Injury Due to T-DXd Analysis

The Kaplan-Meier survival curves for the patients are shown in Figure 1. During the observation period, four patients developed T-DXd-induced lung injury, with a median onset time of 10.32 months (95% Confidence Interval: 9.26-NA).

Table 1. Characteristics of patients and clinical manifestation according to presence or absence of T-DXd-induced lung injury.

	Lung injury group	Non-lung injury	p-value
Number of patients	4	12	
Female (%)	4 (100)	9 (75)	0.53
Age (years)	58.5 (54 - 77)	66.5 (53 - 86)	0.38
eGFR (mL/min/1.73m^2)	73.55 (61.8 - 95.4)	75.8 (45.1 - 122.9)	0.75
SpO_2 (%)	96.5 (96 - 98)	97.0 (92 - 99)	0.66
Dose of T-DXd (mg/kg)	5.4 (5.4 - 5.4)	5.4 (5.16 - 6.4)	1.00
Times of lines	6.5 (5 - 8)	5 (2 - 9)	0.16
Times of courses	13.5 (2 - 15)	5.5 (1 - 22)	0.22
Duration of T-DXd administration (months)	10.6 (1.5 - 11.5)	3.5 (0 - 16.2)	0.17
Breast cancer (%)	4 (100)	10 (83.3)	1.00
Lung comorbidity (%)	0 (0)	0 (0)	1.00

The median values were shown. The data were shown before T-DXd was administered. Times of lines indicate the number of types of chemotherapy until T-DXd was administered, and times of courses indicate the number of times T-DXd was administered. T-DXd, trastuzumab deruxtecan; eGFR, estimated glomerular filtration rate; SpO_2, saturation of percutaneous oxygen.

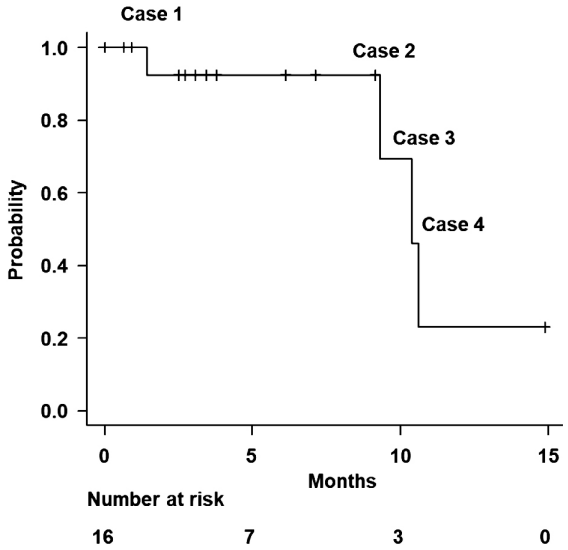


Figure 1. Kaplan-Meier curves for drug-induced lung injury of patients administered trastuzumab deruxtecan. The time of onset of drug-induced lung injury is displayed for the four patients described in this report.

3.3. Case Series

Case 1

A 59-year-old woman presented to our hospital with dyspnea. Eight years ago, she had undergone surgery followed by post-operative radiotherapy for breast cancer. Later, due to a history of breast cancer recurrence, she received drug therapies, including tamoxifen, epirubicin and cyclophosphamide, paclitaxel, capecit-

abine, and eribulin. Dyspnea developed after two courses of T-DXd at a dose of 5.4 mg/kg had been administered to treat recurrent breast cancer, followed by a fifth-line treatment. The body temperature of the patient was 36.7˚C, respiratory rate was 20/min, and her SpO_2 was 97% with 5 L/min oxygen. Chest CT demonstrated ground-glass opacity with a diffuse alveolar damage (DAD) pattern in both lungs (Figure 2(A)-(C)). Blood tests showed elevated lactate dehydrogenase (LD) and c-reactive protein (CRP) levels, but no increase in Krebs von den Lungen 6 (KL-6) levels (Table 2). High-dose steroids were immediately administered (Figure 3(A)). Although the T-DXd-induced lung injury improved, a palliative treatment approach was adopted for managing breast cancer due to the patient's declined performance status.

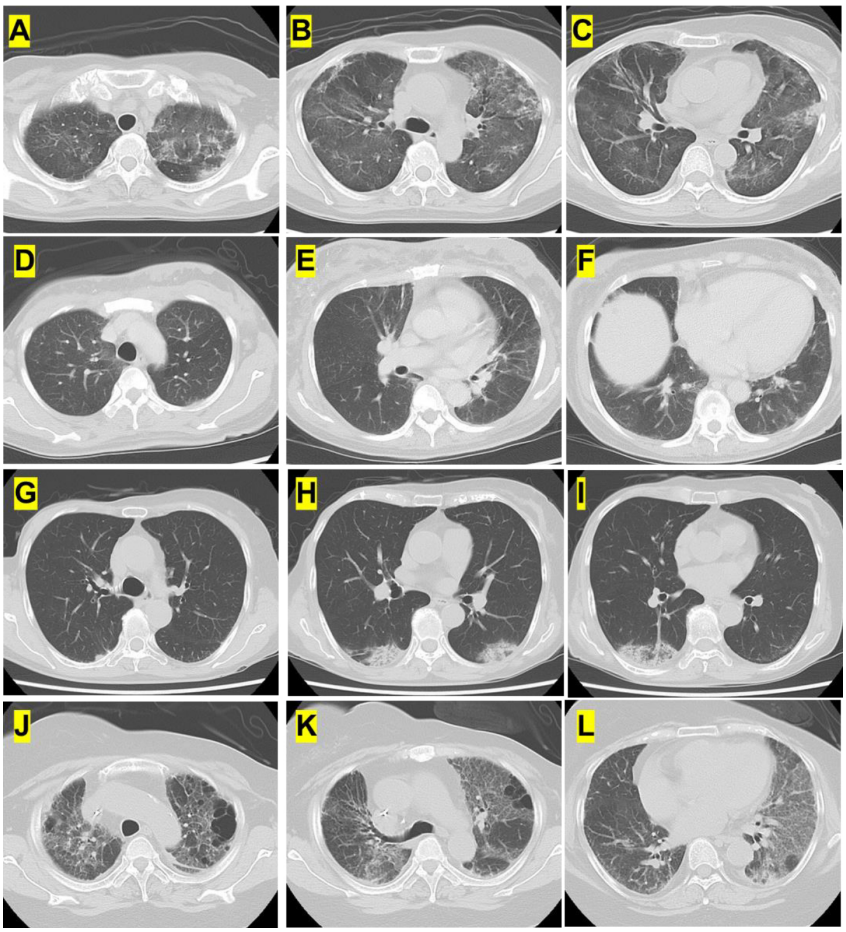


Figure 2. Computed tomography radiographs of the chest in four patients revealed evidence of drug-induced lung injury due to trastuzumab deruxtecan administration. Case 1 (A-C), Case 2 (D-F), Case 3 (G-I), and Case 4 (J-L).

Table 2. Laboratory data.

	Case 1	Case 2	Case 3	Case 4	
WBC	4030	3820	4330	4720	/μL
Neu	84.5	65.8	62.2	68.3	%
Eos	0.0	6.9	1.6	1.3	%

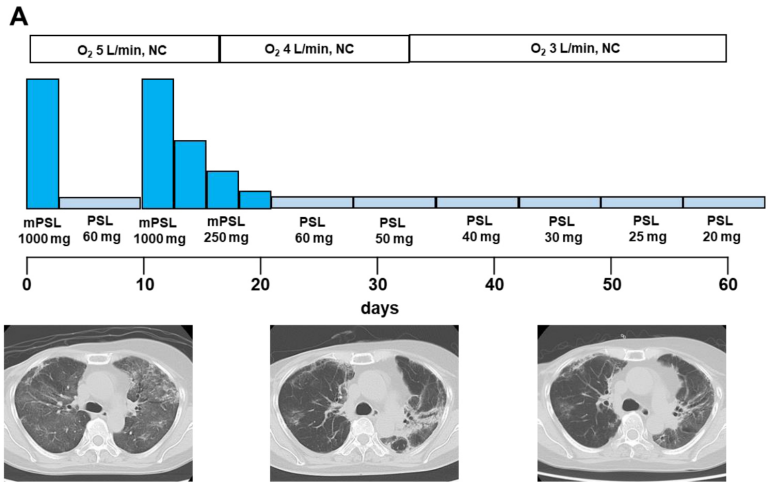
Continued

Bas	0.1	0.2	1.6	0.0	%
Lym	12.8	16.2	22.6	17.3	%
Mo	2.7	10.9	12.1	13.0	%
RBC	371	286	346	228	$\times 10^4/\mu L$
Hb	12.0	10.1	11.7	9.3	g/dL
Plt	10.6	11.1	32.9	6.1	$\times 10^4/\mu L$
Alb	3.5	3.3	3.6	2.9	g/dL
AST	52	41	31	42	U/L
ALT	34	20	22	26	U/L
LD	350	367	244	481	U/L
BUN	13.6	10.5	13.3	23.1	mg/dL
Cre	0.54	0.64	0.81	0.74	mg/dL
CRP	5.44	0.08	0.25	8.44	mg/dL
KL-6	340	1155	298	952	U/mL

WBC: white blood cell count; Neu: neutrophil; Eos: eosinophils; Bas: basophils; Lym: lymphocytes; Mo: macrophage; RBC: red blood cell count; Hb: hemoglobin; Plt: platelet; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LD: lactate dehydrogenase; BUN: blood urea nitrogen; Cre: creatinine; CRP: c-reactive protein; KL-6: Krebs von den Lungen 6.

Case 2

A 54-year-old woman received 13 courses of T-DXd at a dose of 5.4 mg/kg. This was followed by a sixth-line treatment, during which a blood test revealed an elevated KL-6 level of 1155 U/mL. Two years ago, she had undergone surgery and received drug therapies, including docetaxel, trastuzumab and pertuzumab, eribulin and trastuzumab, epirubicin and cyclophosphamide, and letrozole. There were no symptoms, but chest CT demonstrated ground-glass opacity with an organizing pneumonia (OP) pattern in both lungs (Figure 2(D)-(F)). Blood tests revealed elevated levels of LD and KL-6, with no corresponding increase in CRP levels (Table 2). No worsening of the observed shadow was noted via imaging examination, and letrozole was administered 14 days after the diagnosis of T-DXd-induced lung injury.



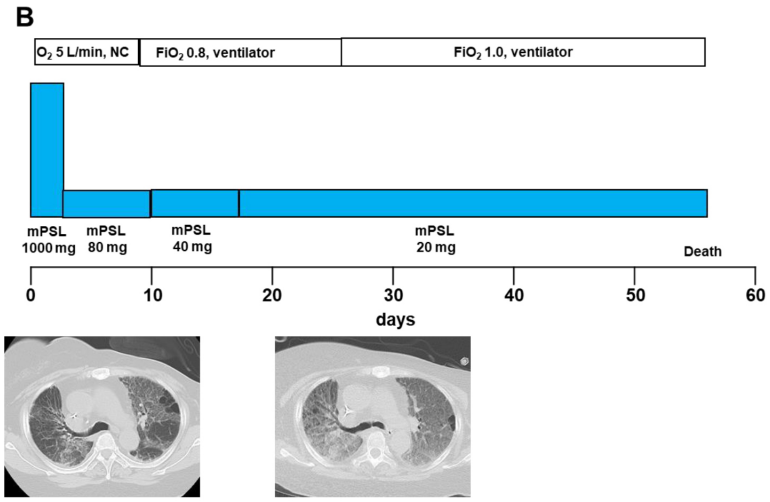


Figure 3. The clinical course of disease in Case 1 (A) and Case 4 (B) is presented. NC: nasal cannula, mPSL: methylprednisolone, PSL: prednisolone.

Case 3

A 77-year-old woman was diagnosed with T-DXd-induced lung injury after an abnormal shadow was incidentally noted during a periodic imaging examination. This occurred while she was receiving 14 courses of T-DXd at a dose of 5.4 mg/kg, followed by a seventh-line treatment. Ten years ago, she had undergone surgery and received drug therapies, including carboplatin and paclitaxel, exemestane, fulvestrant, toremifene, tegafur gimeracil oteracil potassium, eribulin, epirubicin and cyclophosphamide, carboplatin and gemcitabine, fulvestrant and palbociclib. There were no symptoms, and chest CT demonstrated consolidation with an OP pattern that did not align with the bronchovascular bundle, which was situated just below the pleura in both lower lobes (Figure 2(G)-(I)). Blood tests showed no increase in LD, CRP, and KL-6 levels (Table 2). Twenty milligrams of prednisolone were immediately administered. Imaging examination revealed that the shadows had a tendency to improve, so the prednisolone treatment was tapered off. She was administered capecitabine 70 days after being diagnosed with T-DXd-induced lung injury.

Case 4

A 58-year-old woman presented to our hospital with dyspnea and fever. Three years ago, she had undergone surgery and received drug therapies, including pertuzumab, trastuzumab docetaxel, eribulin, and trastuzumab. Dyspnea and fever developed after the administration of 15 courses of T-DXd at a dose of 5.4 mg/kg, followed by an eighth-line treatment. The body temperature of the patient was 36.6˚C, respiratory rate was 24/min, and her SpO_2 was 85% on room air. Chest CT demonstrated ground-glass opacity with a DAD pattern in both lungs (Figure 2(J)-(L)). Blood tests showed elevated LD, CRP, and KL-6 (Table 2). High-dose steroids were immediately administered (Figure 3(B)). The patient was admitted to the intensive care unit for ventilator management; however, respiratory failure worsened, and the patient ultimately passed away.

Four cases of T-DXd-induced lung injury are summarized in Table 3.

Table 3. Characteristics of patients with T-DXd-induced lung injury and their treatment courses.

	Case 1	Case 2	Case 3	Case 4
Age (years)	59	54	77	58
Times of lines	5	6	7	8
Times of courses	2	13	14	15
Dyspnea	Yes	No	No	Yes
Respiratory failure	Yes	No	No	Yes
Imaging pattern	DAD	OP	OP	DAD
Steroid starting dose	mPSL 1000 mg/day	None	PSL 20 mg/day	mPSL 1000 mg/day
Outcome	Palliative care	Improved	Improved	Death

DAD, diffuse alveolar damage; OP, organizing pneumonia; mPSL, methylprednisolone; PSL, prednisolone.

4. Discussion

In this study, we have presented a case series illustrating the frequency of occurrence and severity of T-DXd-induced lung injury and its clinical course. The frequency of occurrence of T-DXd-induced lung injury was 25%, which seems high compared to previous reports [5]-[9]. However, it has been reported that Japanese ethnicity is associated with a 24.4% risk of T-DXd-induced lung injury [10] [11]. Therefore, the frequency of occurrence of T-DXd-induced lung injury reported here may not be particularly high.

A variety of imaging patterns associated with T-DXd-induced lung injury, such as OP, DAD, nonspecific interstitial pneumonia, and hypersensitivity pneumonitis patterns, have been reported based on chest CT. Additionally, cases with a DAD pattern have been associated with a poor prognosis [12]. In this study, there were two cases of T-DXd-induced lung injury that displayed an OP pattern, and two cases exhibited a DAD pattern. In the OP pattern cases, continuing with the next round of chemotherapy was possible; however, continuing chemotherapy was not possible in patients exhibiting a DAD pattern. One of the two patients exhibiting a DAD pattern passed away due to T-DXd-induced lung injury, indicating that the DAD pattern has a poor prognosis, as previously reported.

The clinical backgrounds of the patients were compared based on the presence or absence of T-DXd-induced lung injury, but we observed no significant statical differences, even among parameters that have previously been reported to display differences (Table 1). While it is acknowledged that the sample size in this study is too small to produce statistically significant results, this limitation also suggests that no parameters within this small cohort significantly influenced prognosis.

This study has several limitations. First, it was a single-center, non-randomized, retrospective study. As a result, we were unable to examine all possible prognostic factors or account for selective patient bias. Second, the sample size in this study

is notably small. The Kaplan-Meier survival curves for patients with T-DXd-induced lung injury demonstrated a median onset time of 10.32 months (95% Confidence Interval: 9.26-NA). However, with only four events recorded, the "NA" in the confidence interval presents significant challenges for interpretation and limits the robustness of the findings.

Given the unpredictability of T-DXd-induced lung injury onset (**Figure 1**) and the absence of consistent trends in blood test results (**Table 2**), we deemed it essential to conduct imaging studies following each T-DXd administration. However, we believe that the continued accumulation of studies like this will play a crucial role in advancing the development of more effective strategies for the management of T-DXd-induced lung injury.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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