

Radiation Pneumonitis After Sequential Radiation and Trastuzumab-Deruxtecan: A Case Report and Literature Review

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Abstract

Trastuzumab Deruxtecan (T-DXd) and lung radiotherapy have each been independently associated with pneumonitis. We present a case of a patient with metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-low breast cancer who developed pneumonitis following sequential palliative lung radiotherapy and T-DXd. T-DXd was discontinued, and symptoms resolved after corticosteroids. The literature review identified T-DXd-induced pneumonitis rates of 11.4% across all tumor types and 10.8% in seven breast cancer studies, higher than other anti-HER2 therapies. Additional studies should be done to characterize the risk of combining radiotherapy with T-DXd.

Keywords: Breast neoplasms • Lung diseases • Interstitial • Radiotherapy • Trastuzumab

Introduction

Trastuzumab Deruxtecan (T-DXd or DS-8201a) is a novel antibody-drug conjugate that consists of an anti-human epidermal growth factor receptor 2 (HER2) humanized monoclonal antibody, a tetrapeptide-based 2 cleavable linkers, and a topoisomerase 1 inhibitor payload. The anti-HER2 antibody shares the same amino acid sequence as trastuzumab targeting HER2 receptors in tumor cells. The drug-to-antibody ratio is 8:1, enabling effective delivery of the payload to tumor cells. Within tumor cells, the linker is cleaved by lysosomal cathepsins that are upregulated in cancer cells, thereby releasing the payload. The payload has a high cell membrane permeability, which allows it to diffuse over the target cell membrane and cause cytotoxicity in neighbouring cells regardless of whether they express HER2, resulting in a "bystander effect" [2,3]. T-DXd has demonstrated activity in breast cancer and other tumor types owing to these unique pharmaceutical properties [1-3].

The United States Food and Drug Administration (US FDA) granted accelerated approval to T-DXd on December 20, 2019, for patients with unresectable or metastatic HER2-positive (HER2+) breast cancer who had received two or more prior anti-HER2-based regimens in the metastatic setting based on results from the DESTINY-Breast01 trial and J101

(NCT02564900) [4]. In addition, based on the results of DESTINY-breast04 trial, T-DXd has also been approved for unresectable or metastatic HER2-low (defined as immunohistochemistry 1+ or 2+, in situ hybridization negative) breast cancer in adult patients who have been treated with chemotherapy for metastases or developed recurrence during or within six months of completing adjuvant chemotherapy [5]. T-DXd has also demonstrated intracranial responsiveness in HER2+ breast cancer patients with brain metastases [6-8]. Further, based on these promising results, T-DXd is now being investigated in patients with early-stage breast cancer (NCT04622319). Thus, many breast cancer patients are anticipated to be treated with this agent in the coming years. In T-DXd trials, Interstitial Lung Disease (ILD) and pneumonitis have been identified as important adverse events attributable to therapy [9]. Of note, pneumonitis is also a potential adverse effect of lung Radiotherapy (RT), which is commonly administered in patients with metastatic breast cancer [10]. Further, there can be clinically significant lung exposure following breast and postmastectomy radiotherapy. The safety of lung RT in patients receiving T-DXd has not been prospectively evaluated. We report a case of pneumonitis that developed in the ipsilateral lung after treatment with palliative RT and T-DXd and the results of a literature review assessing pulmonary toxicity following T-DXd.

Case Presentation

A 34-year-old woman presented with a fungating right breast mass, symptomatic regional nodal disease encasing the right brachial plexus, and widespread bone metastases in December 2020. A biopsy revealed metastatic invasive ductal carcinoma of the breast, grade 3, Estrogen Receptor (ER) and Progesterone Receptor (PR) positive, HER2 1+ by immunohistochemistry (i.e. HER2-low), and she was clinically staged T4b N3c M1. She completed three cycles of doxorubicin and cyclophosphamide with a partial response and initiated endocrine therapy consisting of goserelin and letrozole.

After the completion of chemotherapy and approximately four and a half months after diagnosis, the patient received consolidative locoregional RT to 42.56 Gy in 16 fractions, followed by a boost of 10 Gy in 4 fractions to the tumor mass encasing the brachial plexus concurrent with goserelin and letrozole. This led to a significant improvement in right axillary pain and a reduction in the size of the fungating breast mass. Ribociclib was subsequently added to the endocrine therapy regimen and she continued with serial Computed Tomography (CT) scans every 3 months to monitor for progression.

Eighteen months after the initial diagnosis, the patient presented with right-sided pleuritic chest pain, dyspnea and cough. CT of the chest revealed a right infra hilar mass with encasement of the pulmonary vasculature, severe narrowing/stenosis of the right middle lobe bronchus, and post-obstructive changes in the right middle lobe. Transbronchial biopsy of the right middle lobe confirmed metastatic breast carcinoma, ER 81%-90%, PR 51%-60%, and HER2 1+ on immunohistochemistry. She was also noted to have a progression of osseous metastases and new hepatic metastases. T-DXd was recommended and the patient received her first infusion of T-DXd on Day 1 of the first 21-day cycle with a prescription dose of 5.4 mg/kg. She was then referred to radiation oncology and initiated palliative RT to the obstructing right hilar mass two and a half weeks after the T-DXd infusion. The right hilum was treated to 20 Gy in 5 fractions and was completed 18 months after the first course of RT (23 months from initial diagnosis). She also underwent palliative RT to painful pelvic bony metastases at that time (20 Gy in 5 fractions). The doses delivered to the lungs during the first and second RT courses

are summarized in Table 1, and the plan sum dose distribution of both treatment courses is shown in Figure 1.

Table 1. Radiotherapy lung dosimetry

	Ipsilateral lung V20 (Gy)	Total lung V20 (Gy)	Mean total lung dose (Gy)
First RT course (right whole breast, regional nodes, and brachial plexus)	23.10%	12.30%	8.55 Gy
Second RT course (right lung)	6.70%	3.10%	4.20 Gy
Plan sum of first and second courses (separated by 18 months)	51.50%	23.70%	12.88 Gy

RT=radiotherapy

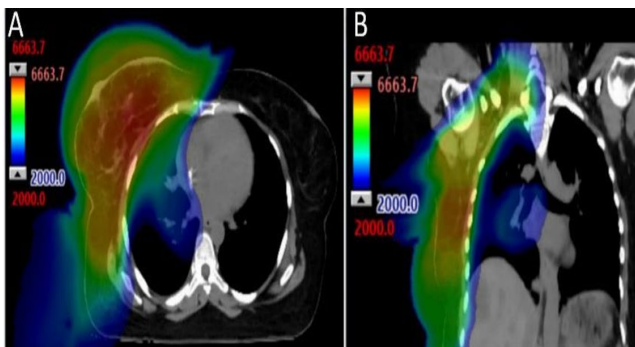


Figure 1. Plan sum colour wash dose distribution from both RT courses in the axial (A) and coronal (B) planes.

During RT, the patient developed bacteremia related to a port infection and was treated with intravenous antibiotics. Thus, the next T-DXd infusion cycle was delayed until two and a half weeks after the completion of RT, and the dose was decreased to 4.4 mg/kg in light of the recent infection. She went on to receive T-DXd cycles 3 and 4. However, approximately two months after completion of RT the patient began experiencing dry cough, dyspnea, and wheezing, with no other signs of infection. CT chest two and a half months following completion of RT demonstrated improved aeration in the right middle lobe, consistent with treatment response, and the development of new multifocal consolidative opacities in the right middle and lower lung (figure 2A). These radiographic findings were within the recent palliative lung RT fields (Figure 2B).

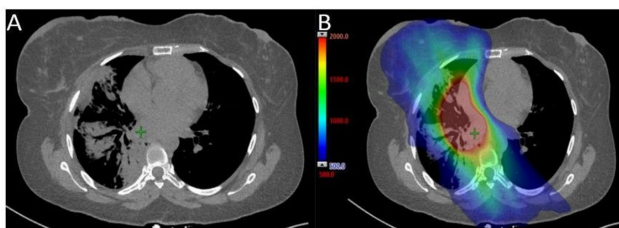


Figure 2. Diagnostic computed tomography of the chest approximately two and a half months following completion of the second course of radiotherapy (A). Colour wash dose distribution from the second course of radiotherapy is shown (B), corresponding to the region of consolidative opacities in the right middle and lower lung.

T-DXd was discontinued, and she was prescribed prednisone 60 mg once daily for clinically diagnosed radiation pneumonitis. Her cough subsided after one week, and prednisone was slowly tapered over the next month. However, on subsequent re-staging at that time she was found to have a progression of liver metastases. Therefore, she was initiated on doxorubicin, but her disease progressed rapidly and the patient developed liver failure and died less than one month later. A timeline of the disease course is displayed in Figure 3.

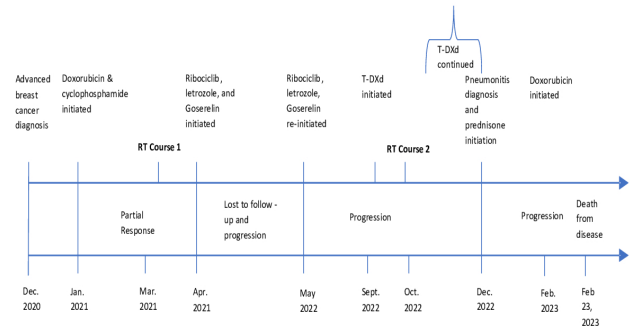


Figure 3. Timeline of disease course, treatment regimens, and development of pneumonitis. RT course 1 = first radiotherapy course, 4256 cGy in 16 fractions with 1000 cGy in 3 fraction boosts. RT course 2 = second radiotherapy course, 2000 cGy in 5 fractions. CT=computed tomography. T-DXd = Trastuzumab deruxtecan.

Discussion

We report a case of pneumonitis in a patient with metastatic breast cancer treated with sequential T-DXd and palliative pulmonary RT. Our literature search revealed the single-agent T-DXd-associated ILD/pneumonitis rate across all solid tumor types combined as 11.4% (all grades) [9] and the rate was 10.8% in seven breast cancer studies [9]. The updated results of the DESTINY breast 01 trial and DESTINY breast 03 trials reported pneumonitis rate with T-DXd as 15.2% and 15% respectively [11,12] and DESTINY breast 02 and 04 trials reporting it as 10% and 12.1% [13,14]. The details of the breast cancer studies reporting pneumonitis rates in participants receiving T-DXd are summarized in Table 2 [11-19]. Apart from breast cancer, the adjudicated ILD/pneumonitis rate was 7.7% in gastric and gastroesophageal junction cancer studies [9], 6.4% (all grade) in colorectal cancer (DESTINY-CRC01 trial) [20], 26.5% (mostly grade 1 or 2) in uterine carcinosarcoma (STATICE trial) [21], and 24.8% in non-small cell lung cancer studies [9]. These ILD/pneumonitis rates with T-DXd are higher than what has been reported with other anti-HER2 therapies [9,22]. For example, in the Katherine trial the incidence of radiation pneumonitis was 1.5% in the T-DM1 arm (740 participants included in safety analysis) and 0.7% in the trastuzumab arm (720 included in safety analysis) [22]. T-DXd-induced ILD/pneumonitis could be fatal [5]. Thus, it is important to identify factors that may increase risk.

Table 2. Rates of interstitial lung disease/pneumonitis in breast cancer patients treated with trastuzumab deruxtecan.

Trial number	Study type	Study population	T-DXd dose	Comparator arm	ILD/pneumonitis rate with T-DXd	ILD/pneumonitis rate in comparator arm	Grade (CTCAE) of pneumonitis
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NCT03248492 (DESTINY breast 01 updated results) [21]	Phase II	HER2+ metastatic breast cancer	5.4 mg/kg q3w		15.20%		Grade 5 (2.7%), other grades are not reported.
NCT03523585 (DESTINY breast 02 trial) [22]	Phase III	HER2+ metastatic breast cancer	5.4 mg/kg q3w	Physician's choice of chemotherapy	10%	<1%	Grade 1 (3%), Grade 2 (6%), Grade 3 (<1%), Grade 4 (0), Grade 5 (<1%)
NCT03529110 (DESTINY breast 03 updated results) [12]	Phase III	HER2+ metastatic breast cancer	5.4 mg/kg q3w	T-DM1	15%	3%	Grade 1 (4%), Grade 2 (10%), Grade 3 (<1%), grade 4 or 5 (0)
NCT03734029 (DESTINY breast 04 trial) [23]	Phase III	HER2-low metastatic breast cancer	5.4 mg/kg q3w	Physician's choice of chemotherapy	12.10%	0.60%	Grade 1 (3.5%), grade 2 (6.5%), grade 3 (1.3%), grade 4 (not reported), Grade 5 (0.8%)
NCT02564900 [24]	Phase I	Advanced/metastatic HER2-low breast cancer	5.4 or 6.4 mg/kg q3w		14.80%		Grade 3 (1.9%), grade 4 (0), grade 5(1.9%), grade 1 and 2 (not reported)
NCT02564900 [25]	Phase I	Advanced/metastatic HER2+ breast cancer	5.4 or 6.4 mg/kg q3w		11.30%		Grade 1 or 2 (5%), grade 3(0), grade 4 (0), grade 5 (2%)
NCT03366428 [26]	Phase I	HER2+/HER2 low metastatic/unresectable breast cancer	6.4 mg/kg q3w		1.90%		Grade 2 only
NCT03368196 [27]	Phase I	Advanced HER2+ breast cancer	6.4 mg/kg q3w		0		-
NCT04752059 (TUXEDO-1 trial) [28]	Phase II	HER2+ breast cancer with brain metastasis	5.4 mg/kg q3w		0		-
HER2+= human epidermal growth factor receptor 2 positive, T-DXd= trastuzumab deruxtecan, T-DM1= trastuzumab emtansine, ILD=interstitial lung disease, CTCAE= common terminology criteria for adverse events, q=every, w=week							

The detailed mechanism for T-DXd-induced pneumonitis has not been fully elucidated, but it has been hypothesized pneumonitis may be related to 1) HER2 receptor expression on the respiratory epithelium that is targeted by T-DXd [23]. T-DXd may in turn damage respiratory epithelium by inhibiting HER2 signalling and/or promoting antibody-dependent cell-mediated cytotoxicity [1]; 2). Direct cytotoxicity of the topoisomerase I inhibitor payload. Upon entry into HER2-expressing cells, the payload gets cleaved via lysosomal enzymes, enters the nucleus, and causes DNA (deoxyribonucleic acid) damage and apoptosis [1,3]; 3) The bystander effect. Due to the high membrane permeability exhibited by the payload, it diffuses across the target cell membrane and enters the neighbouring cells regardless of HER2 expression and may cause normal tissue cytotoxicity [2,3]. Potentially due to this unique mechanism of action, including the "bystander effect" of the topoisomerase I inhibitor payload, T-DXd has resulted in higher rates of pneumonitis as compared to other anti-HER2 therapies [2,9,12,24].

Ionizing radiation causes lung injury via direct or indirect DNA damage leading to cell apoptosis. RT can damage the alveolar barrier and generate an inflammatory response that can lead to radiation pneumonitis [25]. Importantly, topoisomerase I inhibitors are well-established radiosensitizers as they induce replication stress and DNA damage by inhibiting DNA repair machinery [26,27]. Indeed, the T-DXd payload has demonstrated ten times higher inhibitory potency than the active metabolite of a topoisomerase I inhibitor, irinotecan, in cell-free inhibition assays [1], raising the possibility that T-DXd could have radiation response-modifying properties beyond its established single-agent pulmonary effects. That said, no conclusions can be made as to the aetiology of pneumonitis in our patient. Although a mean lung dose of 12.88 Gy would be expected to result in only a modest risk of pneumonitis, not even accounting for normal tissue recovery in the 18 months between RT courses, symptomatic pneumonitis can rarely be observed even after very low doses of radiotherapy [10].

Beyond breast cancer, T-DXd has been approved for the treatment of locally advanced/metastatic HER2-positive gastric/gastro-oesophageal adenocarcinoma and for inoperable or metastatic non-small cell lung cancer with activating HER2 mutations after systemic platinum-based therapy secondary to the findings of DESTINY-Gastric01 trial (NCT03329690) and DESTINY-Lung02 trials (NCT04644237) [28,29]. Additionally, T-DXd has demonstrated efficacy in uterine carcinosarcoma regardless of HER2 status in the STATICE trial and HER2-expressing metastatic colorectal cancer in the DESTINY-CRC01 trial [20,21]. We also found 8 ongoing clinical trials that are

evaluating the safety and efficacy of T-DXd either in combination with other drugs or as a single agent in HER2+ or HER2-low advanced-stage breast cancer patients (Table 3). One of these studies will evaluate the rate of ILD/pneumonitis via investigator assessment and using the St. George's Respiratory Questionnaire (NCT04739761). An additional trial, Destiny 05, is evaluating T-DXd versus T-DM1 in high-risk HER2-positive patients with residual disease following neoadjuvant systemic therapy. T-DXd must begin within 12 weeks of surgery, but the timing with regards to RT is not specified on clinicaltrials.gov.

Table 3. Ongoing clinical trials evaluating the safety and efficacy of trastuzumab deruxtecan.

Study	Trial type	Population	Comparator	T-DXd combined with	Time frame for assessing TEAE
DESTINY breast 05 (NCT04622319)	Phase III (recruiting)	HER2+ early breast cancer with residual disease post neoadjuvant treatment	T-DM1	N/A	81 months
DESTINY breast 06 (NCT04494425)	Phase III (recruiting)	HER2-Low, HR+ breast cancer patients whose disease has progressed on endocrine therapy	Physician's choice chemotherapy	N/A	60 months
DESTINY breast 07 (NCT04538742)	Phase I/II (recruiting)	HER2+ metastatic breast cancer	N/A	durvalumab, pertuzumab, paclitaxel, tucatinib	53 months
DESTINY breast 08 (NCT04556773)	Phase I (active, not recruiting)	HER2-low metastatic breast cancer	N/A	capecitabine, durvalumab, paclitaxel, capivasertib, anastrozole, fulvestrant	24 months
DESTINY breast 09 (NCT04784715)	Phase III (recruiting)	HER2+ metastatic breast cancer	paclitaxel, pertuzumab, trastuzumab	with or without pertuzumab	60 months
DESTINY breast 12 (NCT04739761)	Phase III (recruiting)	Previously treated advanced/metastatic breast cancer with/without brain metastasis	N/A	N/A	2.5 years
HER2CLIMB04 (NCT04539938)	Phase II (recruiting)	Previously treated unresectable locally advanced or metastatic breast cancer	N/A	tucatinib	3 years
TALENT (TRIO-US B-12) (NCT04553770)	Phase II (recruiting)	HR+/HER2 low early breast cancer	N/A	combined with or without anastrozole	6 months

HER2+= human epidermal growth factor receptor 2 positive, HR+= hormone receptor positive, T-DM1= trastuzumab emtansine, T-DXd= trastuzumab deruxtecan, TEAE= treatment emergent adverse events, N/A= not applicable

Conclusion

In summary, pneumonitis is a common adverse effect of T-DXd, which is approved in advanced HER2+ breast cancer and is now being investigated in early-stage disease. Thus, until additional data is available, clinicians should be aware of the individual risk profile of T-DXd and lung radiotherapy, and the theoretical possibility of an additive or synergistic impact on lung injury.

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