



Pulmonary arterial hypertension in breast cancer patients on HER2-targeted therapy: a review of FDA Adverse Events Reporting System data

To the Editor:

The World Health Organization (WHO) classifies drug- and toxin-induced pulmonary arterial hypertension (D-PAH) as a form of Group 1 pulmonary hypertension. Pulmonary arterial hypertension (PAH) refers to pathological remodelling of the pulmonary vasculature, which carries a poor prognosis if left untreated [1, 2]. The incidence and prevalence of PAH observed with therapies that target human epidermal growth factor 2 (HER2) may be underreported. In 20–25% of breast cancers, the chromosomal region that contains the *HER2* gene is amplified, which promotes overexpression of the HER2 receptor tyrosine kinase. Currently, post-marketing studies and case reports associating HER2-targeting agents such as trastuzumab, ado-trastuzumab emtansine (T-DM1), lapatinib and pertuzumab with PAH are rare (<1%), and only trastuzumab has a black box warning for pulmonary toxicity [3–6]. Prompt identification of D-PAH and discontinuation of offending agents is critical to improving outcomes for patients who may be receiving HER2-targeted therapies for breast tumours containing *HER2* gene overexpression.

We report a case of PAH in a woman with HER2-positive stage IV breast cancer who received T-DM1. The patient was a 36-year-old-female who was diagnosed with HER2-positive grade 3 invasive ductal carcinoma in September 2013. She completed three cycles of docetaxel, pertuzumab and trastuzumab, and was transitioned to trastuzumab and pertuzumab alone with complete clinical and radiological response. After >2 years of trastuzumab and pertuzumab-targeted therapy, she underwent palliative mastectomy and continued both agents for an additional 2 years until her disease progressed. She was then switched to T-DM1 in March 2017 and continued this regimen intermittently, with a few treatment holidays due to epistaxis and thrombocytopenia. Her last dose of T-DM1 was in October 2019. Further treatment with T-DM1 therapy was discontinued due to disease progression a month later.

During a routine follow-up visit, she reported shortness of breath associated with fatigue and cough over a period of 3 months prior to the presentation. Her vital signs were concerning for an elevated heart rate and increased respiratory effort. Physical examination revealed jugular venous distention, an accentuated P2 and chest wall telangiectasias. Serological testing was unremarkable. Transthoracic echocardiography discovered a large circumferential pericardial effusion, left ventricular diastolic collapse and a severely depressed right ventricular (RV) function with an estimated pulmonary arterial systolic pressure (PASP) of 102 mmHg, consistent with tamponade physiology. She was urgently admitted and underwent a pericardial window to allow continuous drainage of pericardial effusion noted on echocardiography.

Right heart catheterisation was performed, which confirmed the diagnosis of PAH with a mean pulmonary artery pressure of 39 mmHg, a pulmonary capillary wedge pressure of 9 mmHg, a pulmonary vascular resistance of 6 Wood units (WU) and a negative vasoreactivity test. She had a negative autoimmune work-up, normal ventilation/perfusion scan and a high-resolution computed tomography to identify any other possible cause of PAH. In the absence of any other possible aetiology of PAH, T-DM1



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This letter highlights a rare association of anti-HER2 cancer therapy with development of pulmonary arterial hypertension, based on a review of data from the FDA <https://bit.ly/2X90xDu>

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was considered the offending drug and further treatment with HER2-targeted therapy was withheld. The patient was started on sildenafil and selexipag, and a significant improvement in her respiratory status was noted over the next 10 days. Her follow-up echocardiogram a month post-discharge showed left ventricular ejection fraction (LVEF) 60–69%, normal RV systolic function and pulmonary arterial systolic pressure of 25 mmHg. We utilised the Naranjo algorithm [7] (which is often used clinically to determine the probability of an adverse drug reaction) to identify T-DM1 as the probable cause of PAH. Application of the Naranjo algorithm to our index case resulted in a score of 7 based on symptoms of PAH following a temporal sequence of exposure to T-DM1, lack of alternative causes and confirmation of PAH by objective evidence. Although there is no boxed warning for pulmonary vascular toxicity with T-DM1, it has been associated with the development of PAH in one case report [8]. KWON *et al.* [8] reported symptoms of shortness of breath, fatigue and hereditary haemorrhagic telangiectasia (HHT) in a patient with HER2-positive stage IV breast cancer being treated with T-DM1. Similarly, our patient was diagnosed with severe PAH 2 months after the last dose of T-DM1 but had received this medication over 19 months. She also noticed progressive dyspnoea and fatigue along with the development of telangiectasia on her anterior chest wall. Our patient also had intermittent epistaxis. As previously suggested by KWON *et al.* [8], the presence of HHT and PAH point towards possible mutations in activin receptor-like kinase 1 (*ACVRL1*). However, genetic testing was not performed in our patient since it would not have changed the course of her treatment. Common aetiologies of PAH such as connective tissue disease, portal hypertension, HIV, congenital heart disease and pulmonary embolism [9] were ruled out in this patient.

There are only two published reports describing a total of five patients with PAH induced by anti-HER2 agents: a case with T-DM1 [8] and four cases with lapatinib [9, 10]. Based on our index case, we queried the FDA Adverse Event Reporting System (FAERS) Pharmacovigilance Database and found 22 distinct reported cases of PAH associated with the use of HER2-targeting regimens. We also conducted a disproportionality signal analysis by calculating the reported odds ratio (ROR) of PAH with HER2-targeted therapies from approval to 2019 (table 1). Calculations were based on total numbers of PAH cases (n=9424) and a total number of reported adverse events in FAERS (n=18650676). Only six of the reported PAH cases (<1%) were associated with T-DM1 as the potential cause. Only T-DM1 (ROR 3.34, 95% CI 1.49–7.43) and lapatinib (ROR 2.93, 95% CI 0.83–1.93) were shown to have a significant association with PAH based on RORs. Although the exact mechanism of pulmonary vascular toxicity with these agents is unclear, lapatinib interaction with off-target kinases, disruption of cytoskeletal microtubules and apoptosis of potentially HER2-expressing endothelial cells with T-DM1 have all been suggested as proposed mechanisms [8, 9].

Our patient was not re-challenged with T-DM1. However, she did not experience recurrence of her PAH after re-exposure to trastuzumab and pertuzumab for the progression of metastatic disease. Akin to reported cases, we observed complete resolution of PAH upon withdrawal of T-DM1 and initiation of PAH therapy.

In conclusion, this case highlights a rare but possible association of the development of PAH with the use of HER2-targeted therapy. This is rarely reported in the literature and our review of FAERS data also attests to our observation of this association. Based on our case and a previously reported case [8], it appears that development of PAH in patients on T-DM1 is mediated *via* HHT-like mechanisms, raising a possibility that it might be mediated *via* the *ACVRL1* mutation pathway seen in PAH. The FAERS review revealed many

TABLE 1 Reports of pulmonary arterial hypertension (PAH) in the FDA Adverse Events Reporting System

	T-DM1	Trastuzumab	Pertuzumab	Lapatinib	Total
Total adverse events	3559	27819	8227	4052	34189
Reported PAH cases	6	12	2	6	22 [#]
ROR (95% CI)	3.34 (1.49–7.43)	0.85 (0.48–1.5)	0.48 (0.12–1.92)	2.93 (1.32–6.53)	1.27 (0.83–1.93)

T-DM1: ado-trastuzumab emtansine. ROR: reported odds ratio. [#]: a total number of 22 distinct cases of PAH with HER2-targeted agents as suspected agents were reported: two distinct cases with T-DM1 and trastuzumab listed as potential causes of PAH; one distinct case with trastuzumab and pertuzumab listed as the potential cause of PAH; and one distinct case with pertuzumab and T-DM1 listed as the potential cause of PAH.

such patients. Clinicians should be aware of the potential for PAH with HER2-targeted therapies, and monitor patients receiving these agents closely for signs and symptoms for drug-induced PAH.

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