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Cardiac Safety of Trastuzumab Deruxtecan in HER2-Positive Metastatic Breast Cancer: A One-Year Prospective Echocardiographic Study

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Abstract

Background: Trastuzumab Deruxtecan (T-DXd) is a novel antibody–drug conjugate with proven efficacy in HER2-positive metastatic breast cancer. While its safety profile is generally favorable, data on cardiotoxicity remains limited.

Objectives: To evaluate the impact of T-DXd on cardiac function using comprehensive echocardiographic assessment after one year of therapy.

Methods: We conducted a prospective observational study including 18 patients with HER2-positive metastatic breast cancer treated with T-DXd. All patients underwent transthoracic echocardiography at baseline and after a median follow-up of 12 months. Conventional and advanced parameters were assessed, including Left Ventricular Ejection Fraction (LVEF), Global Longitudinal Strain (GLS), diastolic function, and right ventricular function.

Results: No significant differences were observed between baseline and follow-up in any echocardiographic parameter. LVEF and GLS remained within normal ranges, with no evidence of subclinical or overtly systolic dysfunction. Diastolic and right ventricular parameters also showed no significant changes.

Conclusion: In this cohort, T-DXd demonstrated a favorable cardiac safety profile over one year of treatment. Larger studies with longer follow-up are warranted to confirm these findings.

Keywords: HER2-Positive breast cancer; Trastuzumab deruxtecan; Cardiotoxicity; Echocardiography; Global longitudinal strain.

Introduction

HER2-positive breast cancer accounts for approximately 15-20% of all breast malignancies and is characterized by increased tumor aggressiveness and poorer clinical outcomes compared with HER2-negative disease [1].

The development of Antibody-Drug Conjugates (ADCs) has significantly expanded therapeutic options in this setting, demonstrating substantial efficacy not only in HER2-overexpressing tumors but also in HER2-low breast cancer [2].

Trastuzumab-Deruxtecan (T-DXd) is a next-generation HER2-directed ADC combining a monoclonal antibody with a potent topoisomerase I inhibitor payload. It has shown remarkable clinical activity across multiple HER2-expressing solid tumors, including breast cancer, and is now widely used in the metastatic setting [3].

Despite its favorable efficacy profile, safety concerns remain. The most clinically relevant adverse event associated with T-DXd is interstitial lung disease; however, cardiotoxicity remains a key issue in the broader context of anti-HER2 therapies [4].

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Indeed, HER2-targeted treatments are known to induce left ventricular dysfunction in up to 15-20% of patients, potentially progressing to overt heart failure if not promptly recognized and managed [5]. This is partly explained by the critical role of HER2 signaling in cardiomyocyte survival, homeostasis, and repair [6].

Available evidence suggests that the incidence of cardiotoxicity with T-DXd is relatively low (approximately 1.9%), with asymptomatic reductions in left ventricular ejection fraction (LVEF) representing the most commonly reported manifestation [7]. Nevertheless, real-world data and longitudinal assessments of cardiac function remain limited.

In this context, we aimed to evaluate the impact of T-DXd on cardiac function using comprehensive echocardiographic assessment, including advanced imaging parameters, in patients with HER2-positive metastatic breast cancer after one year of therapy.

Methods

Study population: We conducted a prospective observational study including 18 consecutive patients with HER2-positive metastatic breast cancer treated with Trastuzumab-Deruxtecan (T-DXd). All patients were enrolled at our institution and underwent serial cardiovascular evaluation.

Eligibility criteria included: (1) confirmed HER2-positive metastatic breast cancer, (2) indication to T-DXd therapy according to current clinical practice, and (3) availability of complete echocardiographic assessment at baseline and follow-up.

The protocol was approved by the local ethics committee (refence number: prot 2.2025 POETA study) and conducted in accordance with the principles of the Declaration of Helsinki; all patients signed a written informed consent form to participate.

Echocardiographic assessment: All patients underwent comprehensive Transthoracic Echocardiography (TTE) at baseline, prior to initiation of T-DXd, and after a median follow-up of 12 months.

Echocardiographic studies were performed using a Vivid E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with a 2.5 MHz phased-array transducer, in accordance with the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) [8,9].

The following parameters were systematically collected: Left Ventricular Ejection Fraction (LVEF), assessed using the biplane Simpson method [8], left ventricular mass indexed to height 2.7 (LVMI) [8], Global Longitudinal Strain (GLS) derived from speckle-tracking analysis [9], left ventricular diastolic function, evaluated using transmittal Doppler flow (E/A ratio) and tissue Doppler imaging (septal and lateral e' velocities), Tricuspid Annular Plane Systolic Excursion (TAPSE) [8], Systolic Pulmonary Artery Pressure (SPAP) [8].

All measurements were averaged over three cardiac cycles and analyzed by experienced operators blinded to clinical data.

Statistical analysis: Continuous variables are presented as mean ± standard deviation. Comparisons between baseline and follow-up values were performed using the paired Student's t-test.

A two-sided p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA).

Results

We analyzed eighteen patients at baseline, prior to initiation of T-DXd therapy, and at one-year follow-up. No significant differences were observed in echocardiographic parameters between baseline and follow-up. No evidence of systolic function impairment was detected using either conventional or advanced measures, including GLS, all of which remained within the normal range. Likewise, no significant changes were observed in the morphological or diastolic functional parameters of the left ventricle. Furthermore, right ventricular longitudinal function, assessed by TAPSE, as well as SPAP, showed no significant variation.

Table 1: Static analysis of echocardiographic parameters before and after 12 months of treatment.

Parameters	Basal (N=18)	Follow up (N=18)	P
HR (bpm)	70 + 11	71 ± 11	0,6
SBP (mmHg)	135 ± 1 16	128 ± 19	0,2
BSA (m^2)	1,7 + 0,1	1,7 ± 0,1	0,11
End diastolic LV dimension (mm)	45,7 + 4,9	45,7 ± 4,2	1
RWT	2,2 ± 7,6	2,1 +7,4	0,3
LVMi	40 ± 12	38,7 ± 12	0,4
EF	58,7 + 4,9	59 ±4	0,6
GLS	20,8 ± 2,2	21 ±2,4 ±	0,7
LAVi	29,5 ± 11	31 ± 12	0,2
Ee	7,9 ± 1,7	7,2 ± 2	0,2
SPAP	29,6 + 6,5	26 ± 4,8	0,1
TAPSE	22,7 + 4,4	22 ±2,9	0,6

BSA: Body Surface Area; HR: Heart Rate; EF: Ejection Fraction; GLD: Global Longitudinal Strain; LAVi: Left Atrial Volume Index; LVMi: Left Ventricular Volume Index; LV: Left Ventricular; SBP: Systolic Blood Pressure; RWT: Relative Wall Thickness; SPAP: Systolic Pulmonary Artery Pressure; TAPSE: Tricuspid Annular Plane Systolic Excursion.

Discussion

In this prospective study, we did not observe any significant changes in echocardiographic parameters after one year of treatment with trastuzumab deruxtecan. Both conventional indices, such as LVEF, and more sensitive markers of myocardial function, including GLS, remained stable and within normal ranges, suggesting the absence of both overt and subclinical cardiotoxicity.

These findings are consistent with data from clinical trials, where the incidence of cardiotoxicity associated with T-DXd appears to be relatively low compared with earlier HER2-targeted therapies. In pivotal studies, asymptomatic reductions in LVEF were reported in a small proportion of patients, while clinically significant heart failure events were rare. However, it should be noted that patients enrolled in clinical trials are often highly selected, and real-world evidence remains limited.

The pathophysiological basis of cardiotoxicity in HER2-targeted therapies is related to the inhibition of HER2 signaling in cardiomyocytes, which plays a crucial role in cellular repair and survival. Despite sharing the same target, T-DXd may exhibit a more favorable cardiac safety profile, potentially due to its specific pharmacokinetic and pharmacodynamic properties. Nevertheless, long-term effects and cumulative toxicity remain areas of ongoing investigation.

Importantly, our study incorporated advanced echocardiographic techniques, particularly GLS, which is known to detect early myocardial dysfunction before changes in LVEF occur. The stability of GLS values in our cohort further supports the absence of subclinical cardiac impairment and strengthens the robustness of our findings.

Despite the overall reassuring results, isolated cases of cardiotoxicity have been reported in the literature. For example, a case of symptomatic LVEF reduction was described in a patient undergoing prolonged T-DXd therapy [10], while another report highlighted the development of atrial fibrillation and valvular dysfunction shortly after treatment initiation [11]. Although causality cannot always be definitively established, these observations underline the need for continued vigilance.

From a clinical perspective, our findings support the current recommendations for regular cardiac monitoring in patients receiving HER2-targeted therapies. Periodic echocardiographic evaluation, ideally including GLS assessment, every 3-4 months may allow early detection of potential cardiac dysfunction and timely initiation of cardioprotective strategies.

This study has several limitations. The sample size is small, and the follow-up period, although clinically relevant, may not be sufficient to detect late-onset cardiotoxicity. In addition, the absence of a control group limits the ability to draw definitive conclusions regarding causality.

In conclusion, our data contribute to the growing body of evidence supporting the cardiac safety of trastuzumab deruxtecan. However, larger prospective studies with longer follow-up are needed to better define the long-term cardiovascular risk associated with this therapy.

Conclusion

This study confirms a favorable cardio-oncological safety profile in the use of deruxtecan for the treatment of HER2-positive metastatic breast cancer. However, further studies with larger sample sizes and longer follow-up periods are needed to strengthen and validate the findings of our study.

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