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Cardiotoxicity Associated with Antihuman Epidermal Growth Factor Receptor-2 Therapy: Particular Aspects of a Specific Phenomenon

LETTER TO THE EDITOR

To the Editor,

In the clinical setting, the term "cardiotoxicity" has been mostly used to denote a specific form of cardiomyopathy associated with a variety of chemotherapeutic agents.[1,2] In this context, anthracycline therapy represents the prototype of irreversible cardiotoxicity (type-1), whereas anti human epidermal growth factor receptor 2 (HER2) therapy (comprising agents including trastuzumab and pertuzumab) is widely recognized to induce a specific form of reversible cardiomyopathy (type-2).[1-3] "Overt cardiotoxicity," by gross definition, mostly signifies a fall of >10% point in the left ventricular ejection fraction (LVEF) value eventually ending up with subnormal systolic functions on echocardiogram.[2] The recent article by Şener et al[1] has described a case of anti-HER2 therapy-mediated cardiotoxicity in a young female patient.[1] Accordingly, I would like to underscore particular aspects of this specific phenomenon:

First, cardiotoxicity associated with anti-HER2 therapy mostly emerges in the presence of traditional cardiovascular risk factors such as smoking, hypertension, diabetes, valvular heart disease, etc.[4] Notably, absence of these risk factors in the patient[1] seems quite interesting. Presence of such risk factors mandates more frequent monitoring of patients receiving anti-HER2 therapy for the early detection of overt cardiotoxicity and may also warrant cardioprotective strategies (beta blocker, statin therapy, etc.) even in the absence of "early cardiotoxicity" [an incipient stage preceding overt cardiotoxicity and presenting with normal or near normal left ventricular (LV) systolic functions yet; with significant elevation of biomarkers including cardiac troponins and natriuretic peptides along with disturbances in echocardiographic indices including global longitudinal strain (GLS)].[2,4] I wonder about the levels of these biomarkers and indices (if measured) along with implemented cardioprotective strategies (if any)[2] during the first cycles of anti-HER2 therapy when LVEF values on echocardiogram seemed normal or near-normal. This might uncover whether overt cardiotoxicity in the patient emerged with or without a preceding "early cardiotoxicity" phase and also whether it emerged despite cardioprotective strategies.

Second, cardiotoxicity associated with anti-HER2 therapy is well known to be devoid of ultrastructural changes and has been attributed to a variety of mechanisms including immune-mediated myocardial damage and blockade of myocardial HER2 signaling (leading to blunted myocardial protection, enhanced myocardial inflammation, etc.).[5] Recovery of LV systolic functions usually takes place at 4-6 weeks following the cessation of anti-HER2 therapy.[3] However, cardiotoxicity in this context, as opposed to the general consensus, may not be fully reversible, and may even progress in certain cases despite the cessation of the culprit agent.[3-5] Notably, mechanisms of poor recovery might be multifactorial, and remains to be fully established. Accordingly, the patient may also be considered to have an incomplete LV recovery if her final LV ejection fraction (LVEF) value (50%) fails to demonstrate any further increase on follow up.[1]

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Third, since anti-HER2 therapy confers a strong prognostic benefit in the setting of breast cancer,[3,5] re-initiation of agents including trastuzumab (for the completion of 1-year therapy) may be considered in select patients following complete recovery of LV functions.[4] However, resumption of trastuzumab should be accompanied by heart failure (HF) therapy.[4] Accordingly, I wonder about the current LVEF value in the patient along with the decision of cardiooncology counseling on the re-initiation of anti-HER2 therapy.

Fourth, subtle alterations in the right ventricle (RV) [on magnetic resonance imaging (MRI)] were previously reported in patients receiving trastuzumab in the absence of overt cardiotoxicity.[6] However, therapeutic and prognostic implications of RV involvement are still nebulous in this context.[6] On the other hand, RV may be more frequently and more extensively involved in those with an overt cardiotoxicity than those without. Accordingly, did the patient have signs of RV involvement on MRI or echocardiogram?

Fifth, subepicardial linear late gadolinium enhancement (LGE) has been a typical phenomenon in the overwhelming majority of patients with anti-HER2 therapy-related cardiotoxicity.[3-5] It was previously reported to be evident even after several months, and even in those with a significant recovery of LV systolic functions.[4] However, further characteristics and implications of this LGE pattern (permanence, association with poor LV recovery) need to be established.[4] Would they consider another MRI for LGE re-evaluation? In a recent meta-analysis, the presence of LGE was suggested as a strong and independent predictor of malignant arrhythmogenesis and sudden death in patients with dilated cardiomyopathy.[7] Would they consider Holter monitoring and electrophysiological study for arrhythmia risk-stratification? Interestingly, the patient had a septal LGE involvement[1] in contrast to the previous reports exclusively documenting LGE pattern in the LV lateral wall.[3-5] I also wonder about the authors' comment on this unusual LGE location.[1]

Sixth, optimal HF therapy yields a significant therapeutic benefit in those with cardiotoxicity.[1,8,9] Accordingly, sacubitril-valsartan therapy was previously reported to be associated with a significant LV reverse remodeling in patients with breast cancer suffering chemotherapy-related cardiotoxicity.[8,9] I wonder about the details of optimal HF therapy in the patient. Did they use sacubitril-valsartan therapy?

Finally, reduced exercise capacity due to persistent subclinical myocardial dysfunction and musculo-skeletal toxicity may be likely after full recovery of anti-HER-2 therapy-related cardiotoxicity, potentially leading to poor quality of life.[3,10] Evaluation of certain echocardiographic indices, including GLS[2] and cardiopulmonary exercise testing may uncover such residual abnormalities and indicate further therapeutic strategies including exercise therapy[10] in the patient.

In conclusion, cardiotoxicity due to anti-HER2 therapy might be regarded as a specific and multi-faceted phenomenon with important clinical implications.[1-6] In cardiooncology practice, this phenomenon should always be evaluated and managed from a broader perspective for the improvement of patient outcomes.

REFERENCES

1. Şener YZ, Ardalı Düzgün S, Hazırolan T, Tokgözoğlu L. Cardiac magnetic resonance imaging findings in human epidermal growth factor receptor 2-targeted therapyrelated cardiotoxicity. *Anatol J Cardiol*. 2023;27(12):E38-E39. [CrossRef]
2. Yalta K, Yetkin E, Yalta T. Serum copeptin in cardiooncology practice: review of pathophysiological and clinical implications. *Balkan Med J*. 2023;40(2):82-92. [CrossRef]
3. Jiang J, Liu B, Hothi SS. Herceptin-mediated cardiotoxicity: assessment by cardiovascular magnetic resonance. *Cardiol Res Pract*. 2022;2022:1910841. [CrossRef]
4. Wadhwa D, Fallah-Rad N, Grenier D, et al. Trastuzumab mediated cardiotoxicity in the setting of adjuvant chemotherapy for breast cancer: a retrospective study. *Breast Cancer Res Treat*. 2009;117(2):357-364. [CrossRef]
5. Fallah-Rad N, Lytwyn M, Fang T, Kirkpatrick I, Jassal DS. Delayed contrast enhancement cardiac magnetic resonance imaging in trastuzumab induced cardiomyopathy. *J Cardiovasc Magn Reson*. 2008;10(1):5. [CrossRef]
6. Barthur A, Brezden-Masley C, Connelly KA, et al. Longitudinal assessment of right ventricular structure and function by cardiovascular magnetic resonance in breast cancer patients treated with trastuzumab: a prospective observational study. *J Cardiovasc Magn Reson*. 2017;19(1):44. [CrossRef]
7. Di Marco A, Anguera I, Schmitt M, et al. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail*. 2017;5(1):28-38. [CrossRef]
8. Yalta K, Gok M, Ozturk C, Yalta T. Sacubitril-valsartan: hope or hype in the battle against cardiotoxicity due to cancer treatment? *Kardiol Pol*. 2022;80(9):958-959. [CrossRef]
9. Sławiński G, Jankowska H, Liżewska-Springer A, Lewicka E. Effective cardioprotection with early initiation of sacubitril valsartan in a patient with breast cancer and cancer treatment-induced heart failure. *Kardiol Pol*. 2022;80(7-8):869-870. [CrossRef]
10. Scott JM, Nilsen TS, Gupta D, Jones LW. Exercise therapy and cardiovascular toxicity in cancer. *Circulation*. 2018;137(11):1176-1191. [CrossRef]