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Reply to Letter to the Editor: "Cardiotoxicity Associated with Antihuman Epidermal Growth Factor Receptor-2 Therapy: Particular Aspects of a Specific Phenomenon"

LETTER TO THE EDITOR
REPLY

To the Editor,

We have read the comments[1] about our case[2] and are pleased to have a chance to discuss conflicting points. We had presented a female with human epidermal growth factor receptor (HER2)-positive breast cancer who was complicated by anti-HER2 therapy-related cardiotoxicity.[2] Your comments about the case are invaluable.[1] We summarized the course of the disease briefly due to the limitation of word count. We especially focused on the magnetic resonance imaging (MRI) findings of anti-HER2 therapy-related cardiotoxicity,and so we could not mention the history and management of the case in detail. As you mentioned, anti-HER2-related cardiotoxicity is more frequent in patients with underlying cardiovascular risk factors, and the current guidelines recommend active surveillance follow-up in order to detect the cases with impending cardiotoxicity earlier.[3] Our patient had no additional cardiovascular risk factors, and her diagnosis and treatment course were before the release of the current cardio-oncology guidelines. Therefore, awareness about the surveillance of asymptomatic cancer patients was inadequate, and because she had no cardiovascular risk factors, she had not been referred to the cardiology department until she presented with cardiac symptoms. We don't have the baseline and follow-up levels of cardiac biomarkers and global longitudinal strain as a consequence. We agree that cancer therapy-related cardiotoxicity is more frequent in cases with additional cardiovascular risk factors; however, presence of additional risk factors is not a rule for the development of cardiotoxicity as in our case.

Our patient presented with new onset acute heart failure with reduced ejection fraction, and we administered intravenous furosemide, ramipril 2.5 mg o.d., metoprolol succinate 25 mg o.d. and doubled the doses of ramipril and metoprolol succinate before discharge. We switched ramipril to the sacubitril-valsartan 24/26 mg twice a day (b.i.d.) and added spironolactone 25 mg once a day (o.d.) 2 weeks after discharge. The patient's blood pressure was 90/60 mm Hg, and so we could not increase drug doses due to symptomatic hypotension. Ivabradin 5 mg b.i.d. was also added because of uncontrolled heart rate despite the maximally tolerated dose of metoprolol succinate. We did not add sodium glucose cotransporter-2 (SGLT2) inhibitor because the patient was treated in 2017, and we did not have the evidence about the favorable impact of SGLT2 inhibitors on patients with heart failure. We managed the patient in compatible with the recommendations of 2016 ESC heart failure guidelines.[4]

Temporary interruption of the anti-HER2 therapy is recommended in patients with moderate or severe symptomatic cardiotoxicity. Reinitiation of anti-HER2 therapy may be considered only in cases with an improved left ventricular ejection fraction of over 40% without any symptoms or in patients with a left ventricular ejection fraction still lower than 40% despite maximally tolerated heart failure treatment but without alternative cancer treatment options.[3] Our patient's left ventricular ejection fraction improved up to 50%, and her functional capacity was NYHA II.

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Because she had no alternative cancer treatment option and improved left ventricular functions with only mild symptoms, reduced-dose anti-HER2 therapy was reinitiated.

Anti-HER2-related cardiotoxicity also affects the right ventricle, and it has been demonstrated that anti-HER2 therapy causes changes in right ventricular diameter and volumes.[5] In our patient, right ventricular end-diastolic diameter (RV-EDD) was increased (30 mm), and tricuspid annular plane systolic excursion (TAPSE) was measured as 15 mm at the administration with new-onset heart failure. Cardiac MRI also showed a slightly decreased right ventricular ejection fraction (45%). TAPSE increased to 19 mm, and RV-EDD was reduced to 25 mm during follow-up.

Epicadial late gadolinium enhancement (LGE), especially in the lateral wall, is reported in patients with anti-HER2-related cardiotoxicity, and the presence and persistence of LGE are determined to be associated with arrhythmogenesis, as you mentioned.[6] We performed cardiac MRI to exclude differential causes of the heart failure, and the patient had a widespread metastatic disease with an expected life time shorter than 1 year. Her performance status was also Eastern Cooperative Oncology Group 3 and not suitable for chemotherapy. We performed 24-hour rhythm holter monitoring in order to screen for atrial fibrillation and ventricular arrhythmias, but we could not detect any significant arrhythmias. However, we did not plan a control cardiac MRI or electrophysiologic study due to the poor performance status of the patient and her ineligibility for ICD implantation with the purpose of primary prophylaxis.

We thank very much for your valuable contribution to our case report.

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