How does trastuzumab treatment affect the right ventricle in females with breast cancer?

Breast cancer represents one of the most prevalent malignant diseases and also one of the most frequent causes of cancer mortality in females in the world. More than 20% of invasive breast cancers are characterized by the overexpression of human epidermal growth factor receptor type 2 (HER2), which is unfortunately related to a poor prognosis (1). The American Society of Clinical Oncology guidelines recommended the evaluation of HER2 in every invasive breast cancer, at either the time of diagnosis or recurrence, to guide therapy. Recently, the same society published recommendations about breast cancer management that include treatment with monoclonal antibody therapy with trastuzumab alone or in combination with anthracyclines (2). The reason for favoring trastuzumab lies in the fact that several studies and meta-analyses have proven the reduction of the risk of disease recurrence and improvement of survival among HER2 breast cancer patients.

Animal studies revealed that trastuzumab significantly changes the expression of myocardial genes that are important for DNA repair and cardiac and mitochondrial functions, which are related to impaired left ventricular performance (3). The same investigation showed that trastuzumab stimulates oxidative stress and apoptosis in the myocardium of mice and increases serum levels of cardiac troponin-I and cardiac myosin light chain-1 (3). All of these changes represent molecular mechanisms that could induce myocardial damage in terms of decreased left ventricular (LV) ejection fraction (4, 5), impaired LV mechanics (6), alteration of LV and atrial volumes, and LV systolic dysfunction in patients treated with trastuzumab (7).

The results of the right ventricular (RV) remodeling in female patients with breast cancer treated with monoclonal antibody therapy are more controversial. Lange et al. (7) studied cardiac remodeling in female patients with breast cancer before trastuzumab treatment and 3 and 6 months after therapy initiation and reported no difference in diameters of the RV and right atrium, RV systolic pressure, tissue Doppler parameters of RV systolic and diastolic function, tricuspid annular plane systolic excursion (TAPSE), or RV Tei index, which represents the indicator of RV global function. The most recent investigation by Kılıçaslan et al. (8), published in Anatolian J Cardiol on April 2, 2014, entitled demonstrated the deterioration of RV function in patients treated with trastuzumab. Grover et al. (9) enrolled 46 women requiring anthracyclines- and/or trastuzumab-containingchemotherapy regimens for breast cancer and used serial CMR imaging at baseline and 1, 4, and 12 months following chemotherapy in order to evaluate LV and RV volumes and function. These investigators revealed that LV end-systolic volume already increased after the first month and continued to increase progressively until the end of the study (12 months following chemotherapy). On the other hand, LV ejection fraction was reduced in the same direction (9). The same changes were observed on the right side of the heart. Namely, RV end-systolic volume progressively increased, while RV ejection fraction, estimated by MRI, decreased progressively from baseline to the last visit-12 months following chemotherapy (9).

This recent study, published in the Anatolian J Cardiol on April 2, 2014 by Kılıçaslan et al. (8), reported that TAPSE was decreased, and RV myocardial performance index, the Tei index, and tricuspid E/e' ratio were increased after trastuzumab treatment, while median serum NT-proBNP levels, troponin I, and hs-CRP levels were similar between the groups. Additionally, the authors revealed that LV ejection fraction and TAPSE were negatively correlated with the dosage of trastuzumab (8). Interestingly, the investigators did not find any significant difference in LV parameters (transmitral E/A and E/e' ratios, LV Tei index, LV ejection fraction) before and after the treatment, as previous studies reported (4-6); furthermore, there was no difference in BNP, troponin, and CRP before and after trastuzumab therapy.

These findings regarding the RV are in line with previously published results by Tanındı et al. (10), who investigated females with breast cancer who were treated with different chemotherapeutic protocols, which indeed did not include trastuzumab. However, the researchers found significant deterioration of RV systolic and diastolic function, as well as dilatation of the RV and right atrium.

On the other hand, Dores et al. (11) did not detect significant deterioration of LV ejection fraction, but the authors found impairment of LV diastolic function in females with advanced HER2-positive breast cancer who were treated for 3 months with trastuzumab. These investigators did not find a difference in TAPSE or RV systolic pressure after trastuzumab therapy. However, the authors included a relatively small number of subjects and followed the patients for only 3 months, and an echocardiographic evaluation was not made at exactly the same time, which could interfere with the results. Additionally, the

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investigators used a limited number of parameters of RV remodeling.

A previous investigation showed that RV adapts better to volume overload than LV and might tolerate volume overload for a long time without any significant symptoms (12). Although RV deterioration did not change the treatment regimen of the patient, Kılıçaslan et al. (8) demonstrated that trastuzumab could affect the RV before the LV. The authors suggested that decreased TAPSE and increased E/e' ratio and RV Tei index values could be used as markers of trastuzumab-induced cardiac toxicity in this population of patients (8).

A possible reason for the RV impairment in patients after trastuzumab therapy is the thinner structure of the RV, with a smaller number of myofibrils, which makes it more vulnerable to damage by chemotherapy. This was supported by the significant relationship between early myocardial edema and the decline in RV function in 12 months, which was not demonstrated with LV function (9).

The importance of RV function and RV hypertrophy is associated with the risk of heart failure or death (13, 14), which is why the assessment of RV remodeling is very important in patients who receive trastuzumab. The echocardiographic evaluation of the RV is not simple, due to unique geometry and anatomic position; thus, the findings by Kılıçaslan et al. (8) are very important, because they demonstrate that we can use traditional echocardiographic parameters, such as TAPSE, E/e', and the Tei index in the determination of trastuzumab-induced RV impairments. Additionally, these parameters, as surrogate markers of subclinical RV remodeling, could also be used for the evaluation of the improvement of RV function during follow-up, which is essential for this population. At the end, we would like to emphasize that LV and RV parameters in patients who are treated with trastuzumab are mainly in the normal range but still deteriorated in comparison with controls or patients before treatment.

Further investigations should involve a larger number of females with breast cancer who are treated with trastuzumab and include new echocardiographic techniques, such as two- and three-dimensional speckle tracking imaging and three-dimensional echocardiography, which could provide us with comprehensive insights into RV mechanics and function in patients who are treated with chemotherapy.

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