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New-Onset Heart Failure in Association With Severe Hypertension During Trastuzumab Therapy

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Abstract

Heart failure is a dreaded complication of trastuzumab therapy in women with breast cancer overexpressing the human epidermal growth factor receptor (HER)-2. Experimental studies have pointed out that the HER-2 signaling pathway is important in the adaptation to high afterload conditions and its inactivation leads to cardiac decompensation. Herein, we report on 2 patients with breast cancer who were receiving trastuzumab monotherapy and required hospital admission for new-onset heart failure. This occurred at a time of unprecedented blood pressure elevations, in one case due to cessation of antihypertensive medications and in the other case due to a scleroderma crisis. Although trastuzumab may not have been the precipitating factor for blood pressure dyscontrol in these patients, severe, uncontrolled hypertension may have been the precipitating factor for trastuzumab-related acute heart failure. These 2 cases add to previous reports recognizing systemic hypertension as a risk factor for the development of trastuzumab cardiotoxicity and translate experimental observations of the significance of the HER-2 signaling pathway to the bedside. Pending further confirmation, the present observations may raise awareness of the need for appropriate monitoring and control of systemic hypertension in patients receiving trastuzumab, or potentially any other HER-2–targeted therapy.

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The advent of targeted therapy has radically changed the modern-day practice of oncology, tailoring and improving the care of patients with cancer according to specific molecular thumbprints. As an example, trastuzumab, a monoclonal antibody that targets the human epidermal growth factor receptor (HER)-2, has dramatically improved survival rates of women with HER-2 positive breast cancer. However, with this therapeutic gain came the unanticipated loss of cardiac function and the development of clinical heart failure in nearly 30% of the patients when trastuzumab was given concurrently with anthracycline-based therapy.[1] Currently, standard (neo)adjuvant treatment regimens pair trastuzumab with taxane-based chemotherapy and are administered sequentially, either before or after anthracycline-based chemotherapy. There is an incidence of less than 3% of symptomatic heart failure associated with these regimens.[1] Anthracycline-sparing regimens are also being increasingly used to mitigate the cardiac toxicity risk; however, the impact of withholding anthracyclines on breast cancer clinical outcomes remains to be defined.[2,3]

Intriguingly, the unanticipated occurrence of trastuzumab-induced cardiomyopathy has led to novel insights into the role of HER-2 signaling in the myocardium and the discovery of the crucial interaction between endothelial cells and cardiomyocytes. Endothelial cells express neuregulin-1, which binds to HER-3 followed by dimerization with HER-2, leading to the stimulation of the prosurvival, prohypertrophic Akt/ERK pathway and the antiadrenergic nitric oxide pathway.[4] This axis is up-regulated by mechanical strain, and its stimulation has been documented with the development of left ventricular hypertrophy.[4] Conversely, the inhibition of this pathway has been associated with the development of heart failure.[5] In fact, mice with targeted mutation of the epidermal growth factor receptor (ErbB) 2, the murine equivalent of HER-2, develop a cardiomyopathy type that is similar to the one observed in patients with trastuzumab-induced cardiomyopathy.[6] These mice are very well compensated unless subjected to pressure overload.[6] To date, there have been no equivalent clinical reports, that is, individual

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patients developing trastuzumab-induced heart failure during times of prominent blood pressure elevations. This is despite the fact that hypertension has been recognized as a risk factor for trastuzumab-induced cardiomyopathy.[7-9]

Herein, we report on 2 patients who were both receiving trastuzumab monotherapy and required hospital admission for decompensated heart failure of new onset at a time of severely elevated blood pressures. In one case, this was due to cessation of antihypertensive medications, and in the other case, this was related to scleroderma crisis. Although trastuzumab may not have been the precipitating factor for the blood pressure dyscontrol in these patients, their blood pressure dyscontrol may have been the precipitating factor for trastuzumab-related acute heart failure. Thus, they may serve as an illustration of the translation of observations from the bench to the bedside and are hypothesis generating for future cohort studies.

CASE 1

The first case is of a 50-year-old woman with a remote 30 pack-year history of smoking and seizure disorder who was diagnosed with premenopausal right-sided stage IIA breast cancer. The tumor was 20% estrogen receptor (ER) and 15% progesterone receptor (PR) positive; HER-2 was strongly amplified with a HER-2 to D17Z1 ratio of 8.3. She underwent bilateral mastectomy but declined adjuvant chemotherapy and endocrine therapy. After 1.5 years, she was diagnosed with diffuse systemic scleroderma and was found to have multiple liver metastases of breast primary (ER and PR negative, HER-2 positive). She was initially treated with weekly doses of paclitaxel and trastuzumab; however, paclitaxel was discontinued after 1 dose because of intolerable adverse effects. After 26 weekly doses of trastuzumab and a nearly complete response (by imaging), she developed grade 3 allergic dermatitis in regions of her body most significantly affected by scleroderma and was advised to discontinue trastuzumab. Subsequent trials of low-dose metronomic cyclophosphamide, methotrexate, and single-agent lapatinib were endured only briefly because of rash and poor tolerance. After a hiatus of approximately 9 months, she opted to restart trastuzumab in view of rapid progression of metastatic breast cancer. After 6 doses of trastuzumab, she developed lower extremity edema, orthopnea, and chest tightness. Chest computed tomography showed cardiogenic pulmonary edema with small bilateral effusions (Figure 1). N-terminal probrain natriuretic peptide level was elevated at 5228 pg/mL, and cardiac troponin T level was elevated at 0.05 ng/mL without significant delta. The 12-lead electrocardiogram (ECG) showed normal sinus rhythm at 98 beats/min without specific changes. An echocardiogram documented an ejection fraction (EF) of 47%, which was a substantial decrease from 60% to 64% on previous echocardiograms. Mild to moderate mitral regurgitation was present, and right ventricular systolic pressure was estimated at 50 mm Hg. In addition to the acutely decompensated heart failure, severe hypertension and renal insufficiency were new to the patient. At the time of her presentation to the emergency department (ED), a blood pressure of 176/107 mm Hg was recorded (maximum 185/112 mm Hg). Blood pressure readings had been in the normal to low normal range (80-90 mm Hg systolic and 60-65 mm Hg diastolic) until the second treatment period with trastuzumab when they gradually increased (Figure 2). Given the concomitantly worsening renal function (increase in serum creatinine to 1.1 mg/dL from a baseline value of 0.6 mg/dL, normal sediment, and proteinuria of only 335 mg/d predicted), a rheumatology evaluation

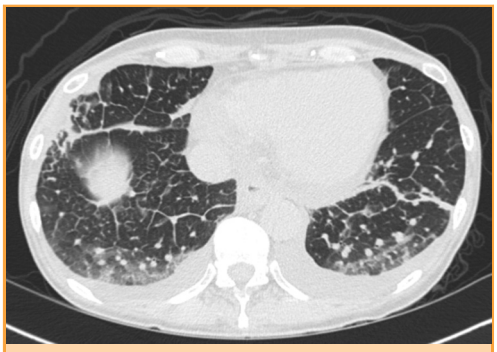

FIGURE 1. Chest computed tomography showing intralobular septal thickening with bilateral patchy areas of groundglass opacities and peribronchial cuffing, most prominent in the mid and lower lungs, and small bilateral pleural effusions, consistent with cardiogenic pulmonary edema.