

## LETTER TO THE EDITOR

### Irreversible cardiotoxicity after adjuvant treatment with trastuzumab in a case of breast cancer

Paolo Bordin, Carla Volpe, Gianna Adami, Valentino Moretti, and Paola Ermacora

*Department of Medicine, Ospedale di San Daniele del Friuli, Udine, Italy*

**To the Editor:** The debate about the cardiotoxicity of trastuzumab remains alive in the literature. In patients with human epidermal growth factor receptor type 2 (HER2) positive breast cancer, trastuzumab has significantly improved the overall survival and is the gold standard treatment in association with chemotherapy. Cardiotoxicity, expressed as a decrease in the left ventricular ejection fraction (LVEF), is not rare with trastuzumab: it occurs in 7% of patients when used as a single agent, peaking up to 27% when it is combined with anthracyclines. The cardiotoxicity is, however, usually reversible<sup>1</sup>.

We describe the case of a 45-year-old woman with synchronous bilateral invasive breast cancer (right pT2N3aMx, left pT1cN0Mx), hormone receptor positive and HER2 positive, without evidence of metastases at staging tests. She underwent surgical therapy followed by adjuvant chemotherapy with doxorubicin plus paclitaxel (6 courses, standard dose) and radiotherapy to the thoracic wall, until December 2005. She started adjuvant therapy with letrozole 2.5 mg plus trastuzumab (loading dose 4 mg/kg, then 6 mg/kg every 3 weeks) in January 2006.

Echocardiography at baseline and in January 2006 was normal (LVEF 55%). In April, asymptomatic myocardial dysfunction developed (LVEF 45%), with negative restaging tests. Trastuzumab was stopped and letrozole maintained. Two months later, the woman was admitted for heart failure. A computed angiotomography scan excluded pulmonary embolism, while echocardiography showed a dilated and severely hypokinetic left ventricle (LVEF 24%). She responded to standard therapy with furosemide, ramipril, carvedilol and an aldosterone antagonist. An echocardiogram 2 weeks later showed an apical thrombus and treatment with warfarin was started. During the following months, she remained eupneic at rest, with persistent sinus tachycardia. In August the LVEF was 20%; a total body positron emission tomography/computed tomography scan showed no signs of cancer. At follow-up 5 months later, the heart function did not show any improvement despite full cardiac therapy. She received an implantable cardioverter defibrillator.

This patient was treated according to standard protocols for invasive breast cancer. All drugs employed (doxorubicin, paclitaxel, trastuzumab and letrozole) are potentially cardiotoxic.

Long-term follow-up studies show that overt heart failure occurs in 4.5% to 7% of patients treated with anthracyclines; it is usually irreversible and dose-dependent, and it may develop after the termination of drug treatment, even years later<sup>2</sup>. The delayed onset of heart damage underlines the limits of monitoring LVEF during anthracycline therapy.

Trastuzumab caused heart failure in 1.7% of patients in the HERA trial; it was dose-independent, developed during treatment or a few months after its stop, and was considered reversible. In the B-31 trial, 31 women (4%) in the trastuzumab group (anthracycline before trastuzumab) had congestive heart failure; only one reported persistent symptoms of heart failure at the last follow-up visit. Ewer reported recently that patients who experienced cardiotoxicity while receiving trastuzumab generally recover their cardiac function when the drug is discontinued (mean recovery time 1.5 months). He observed 38 women over a 4-year period; all patients were treated with anthracyclines before or during treatment with trastuzumab<sup>1</sup>. The incidence of cardiotoxicity among patients treated outside of a clinical trial is not known. McArthur observed cardiac events in 22% of a group of women treated with trastuzumab sequentially after primary chemotherapy with paclitaxel and doxorubicin, but in most cases heart damage was transient and asymptomatic<sup>3</sup>.

Trastuzumab binds to the extracellular domain of the HER2 protein, thereby blocking the ErbB2 signaling that is required for the growth, repair and survival of cardiomyocytes. HER2 activates various transcription factors including AP-1, which is involved in regulating cardiac hypertrophy, and nuclear factor-kappa B, which is involved in the cellular response to stress. ErbB2 signaling in cardiac muscle cells is fundamental for the prevention of dilated cardiomyopathy<sup>4</sup>. Sequential stress may be another mechanism involved in myocardial dysfunction. The incidence of chemotherapy-induced cardiotoxicity could be higher in patients with previous factors promoting left ventricular dysfunction (eg hypertension or ischemic heart disease). In the same way, subclinical myocardial damage may have already oc-

---

Received August 13, 2007; accepted February 8, 2008.

*Correspondence to:* Paolo Bordin, Ospedale di San Daniele del Friuli, V. Trento e Trieste 2, 33038 San Daniele del Friuli, Udine, Italy. Tel +39-0432-949463; fax +39-0432-949493; e-mail paolo.bordin@ass4.sanita.fvg.it

curred in patients treated with anthracyclines before receiving trastuzumab<sup>5</sup>.

Our patient was younger than 60 and had no previous heart disease; her only risk factor for cardiac disease was the use of chemotherapy. She had regular cardiac follow-up and her heart function was still normal at the beginning of therapy with letrozole and trastuzumab. Ventricular dysfunction developed shortly after the start of trastuzumab and progressed irreversibly despite the prompt withdrawal of the drug and optimal cardiac therapy. We do not know which drug is most responsible for this cardiac event, but the association of several potentially cardiotoxic drugs probably results in a major risk factor. This case is unusual for the precocity of the cardiac damage, its worsening and irreversibility after the interruption of drug treatment, and the early complication of a left ventricular thrombus in a patient without risk factors for heart disease nor signs of cancer recurrence.

In clinical practice we are faced with diagnostic problems: some patients can remain asymptomatic despite a significant decrease in LVEF, others have symptoms with a normal LVEF (diastolic heart failure). Moreover, echocardiography is limited by its poor reproducibility and high variability. For this reason, increasing use is made of radionuclide ventriculography, which is highly reproducible with low inter- and intraobserver variability<sup>6</sup>.

Other tests may reveal cardiotoxicity in a more sensitive manner than LVEF. Ongoing trials are evaluating the role of serial B-type atrial natriuretic peptide measurements in the diagnosis and management of heart failure, but at the moment BNP cannot be used as a tool for follow-up<sup>6</sup>. Another hypothesis under investigation concerns cardiac troponin I, the elevation of which seems correlated with the cumulative dose of doxorubicin. Cardiac troponin is released after just one cycle of chemotherapy and the rate of abnormal values increases with each cycle in patients who eventually develop systolic dysfunction<sup>7</sup>. The main advantages of troponins are their high specificity and sensitivity, wide diagnostic window and the possibility to use commercially available assays in clinical settings; the drawbacks are a lack of standardization among the different immunoassays available for troponin and the complex determination of the optimal timing of sample collection, which may be drug-dependent. It is important to note that no histopathological features that would distinguish trastuzumab-associated myocardial injury from anthracycline-induced damage have been identified in the endomyocardial biopsies performed<sup>1</sup>.

Trastuzumab is a cornerstone drug, but its cardiotoxicity in women treated in clinical practice is not well

known and could be more serious than reported in clinical trials<sup>3</sup>. Several ongoing trials are testing strategies to minimize cardiac dysfunction: trastuzumab plus anthracyclines in a less cardiotoxic formulation (eg liposomal doxorubicin) or trastuzumab therapy of short duration in the adjuvant setting<sup>8</sup>. At the first evidence of a slight decrease in LVEF during anticancer therapy, even asymptomatic patients probably benefit from ACE inhibitors and/or beta blockers to contrast its progression to overt heart failure<sup>6</sup>.

Given that heart failure is unpredictable in terms of timing and severity, this case shows us the importance of clinical follow-up scheduled and prolonged over time, as well as the importance for the patient to know the risk/benefit ratio of the offered treatment.

## References

1. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, Lenihan DJ: Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment. *J Clin Oncol*, 23: 7820-7826, 2005.
2. Jensen BV: Cardiotoxic consequences of anthracycline-containing therapy in patients with breast cancer. *Semin Oncol*, 33: S15-21, 2006.
3. McArthur HL, Chia S: Cardiotoxicity of trastuzumab in clinical practice. *N Engl J Med*, 357: 94-95, 2007.
4. Speyer J: Cardiac dysfunction in the trastuzumab clinical experience. *J Clin Oncol*, 20: 1156-1157, 2002.
5. Ewer MS, Gibbs HR, Swafford J, Benjamin RS: Cardiotoxicity in patients receiving trastuzumab (Herceptin): Primary toxicity, synergistic or sequential stress, or surveillance artefact? *Semin Oncol*, 26: 96-101, 1999.
6. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LE, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society: ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, 112(12):e154-235, 2005.
7. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, Civelli M, Peccatori F, Martinelli G, Fiorentini C, Cipolla CM: Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation*, 109: 2749-2754, 2004.
8. Chia S, Clemons M, Martin LA, Rodgers A, Gelmon K, Pond GR, Panasci L: Pegylated liposomal doxorubicin and trastuzumab in HER-2 overexpressing metastatic breast cancer: A multicenter phase II trial. *J Clin Oncol*, 24: 2773-2778, 2006.