Detection of Profound Myocardial Damage by Cardiac MRI in a Patient with Severe Cardiotoxicity Induced by Anti-HER2 Therapy

Hiroshi Kadowaki,
Junichi Ishida,
Masae Uehara,
Arhiro Kiyosue,
Masaru Hatano,
Shogo Shimada,
Minoru Ono,
Hiroshi Akazawa,
and Issei Komuro

Summary

Anti-HER2 therapy has greatly improved the long-term prognosis of patients with HER2-positive breast cancer. Meanwhile, by interfering with the protective effects of neuregulin-1/HER2 signaling on stressed cardiomyocytes, anti-HER2 therapy occasionally induces reversible cancer therapeutics-related cardiac dysfunction (CTRCD). Cardiac magnetic resonance (CMR) parametric mapping or myocardial feature-tracking, in combination with late gadolinium enhancement (LGE) imaging, has the potential to detect changes in the myocardium in anti-HER2 therapy-related cardiac dysfunction. Here we report a breast cancer patient who experienced life-threatening CTRCD after treatment with trastuzumab plus pertuzumab. This case showed multiple transmural LGE-positive myocardial lesions in CMR imaging and high native T1 and T2 values in CMR parametric mapping, which was apparently more extensive than those observed in most patients with anti-HER2 therapy-related cardiac dysfunction. Consistent with profound myocardial damage indicated by CMR, her cardiac function was not fully restored despite intensive care and cardioprotective drug therapy. These findings suggest the potential usefulness of LGE imaging and parametric mapping by CMR for the assessment of myocardial injury to determine the clinical severity of anti-HER2 therapy-related cardiac dysfunction.

Key words: Anthracycline, Breast cancer, Cancer therapeutics-related cardiac dysfunction, Late gadolinium enhancement, Parametric mapping, Pertuzumab, Trastuzumab

Human epidermal growth factor receptor (HER) 2 protein overexpression and/or HER2 gene amplification occurring in breast cancer and gastric cancer promote aggressive tumor growth, and HER2-positive breast cancer is associated with a higher risk of recurrence and poor prognosis. The development of trastuzumab, a monoclonal antibody against HER2 protein, has greatly improved the long-term prognosis of patients with HER2-positive breast cancer. Meanwhile, by interfering with the protective effects of neuregulin-1/HER2 signaling on stressed cardiomyocytes, trastuzumab occasionally induces cancer therapeutic-related cardiac dysfunction (CTRCD). Pertuzumab is a recombinant monoclonal antibody binding to a distinct epitope, which inhibits hetero-dimerization between HER2 and other HER family members. Pertuzumab in combination with trastuzumab interferes with the HER2 signaling more effectively than trastuzumab alone. A clinical trial reported that pertuzumab, when given with trastuzumab and standard chemotherapy, improved invasive-disease-free survival compared with placebo plus trastuzumab and standard chemotherapy, without increasing the incidence of CTRCD in node-positive operable breast cancer patients. Generally, anti-HER2 therapy-related CTRCD is reversible. However, patients are at high risk for developing CTRCD, especially those who have previous anthracycline treatment and cardiac comorbidities and risk factors, and some of them develop severe and irreversible CTRCD. Therefore, it is important to establish strategies for the qualitative and quantitative assessment of myocardial injury relating to disease severity and reversibility in patients receiving anti-HER2 therapy.

Cardiac magnetic resonance (CMR) offers a superior capability of myocardial tissue characterization. Late gadolinium enhancement (LGE) can identify myocardial edema or scarring, which is indicative of irreversible cardiac damage. The accumulation pattern of LGE in the myocardium is helpful to determine the etiology of the underlying disease, and the extent of LGE burden is correlated with the disease severity in various heart diseases. In the field of cardio-oncology, several studies reported that subepicardial linear LGE in the lateral wall of the left ventricle (LV) was a typical finding in patients with trastuzumab-related cardiac dysfunction, and that
the estimated incidence of subepicardial LGE was high, ranging between 94% and 100%, at the end of treatment with anthracyclines plus trastuzumab. Recently, native T1 mapping capable of evaluating intrinsic signals from both myocardium and interstitium has emerged as a promising technique that detects early interstitial myocardial fibrosis with high sensitivity and complements the limitations of LGE, which has less sensitivity to diffuse fibrosis. Pre- and post-contrast T1 mapping allows for estimation of extracellular volume (ECV), which quantifies increased collagen content more accurately with expansion of the extracellular space. T2 mapping also enables quantitative assessment of parameters indicative of diffuse myocardial edema. CMR parametric mapping or myocardial feature-tracking, in combination with LGE imaging, has the potential to detect early changes in the myocardium in trastuzumab-related cardiac dysfunction.

Here we report a breast cancer patient who experienced a fatal course of CTRCD after treatment with trastuzumab plus pertuzumab, which was accompanied by multiple transmural LGE-positive myocardial lesions in CMR imaging and high native T1 and T2 values in CMR parametric mapping. These findings suggest the potential usefulness of LGE imaging and parametric mapping by CMR for the assessment of myocardial injury to determine the clinical severity of anti-HER2 therapy-related cardiac dysfunction.

Case Report

A 37-year-old woman with no medical history underwent total mastectomy with axillary lymph node dissection for HER2-positive left-sided breast cancer (pT2N1M0, stage IIIB), and then received 4 cycles of doxorubicin (total 240 mg/m²) plus cyclophosphamide (total 2,400 mg/m²) regimen (AC regimen). Echocardiographic examination showed a 68% LV ejection fraction (EF) with no wall motion abnormalities (Table). Trastuzumab and pertuzumab plus paclitaxel were administered in an adjuvant setting (total trastuzumab 50 mg/m² and pertuzumab 3,780 mg/body). After the 8 cycles of the treatment, she was transported to an ambulance because of progressive dyspnea and cold sweat. An electrocardiogram showed sinus tachycardia (heart rate 111 beats/minute), and chest x-ray examination revealed severe conges-
tion in bilateral lungs (Figure 1). Biochemical examination showed an elevated level of B-type natriuretic peptide (250 pg/mL) and high sensitivity troponin I (128 ng/L; normal < 15 ng/L) with normal kidney function (blood urea nitrogen 13.3 mg/dL and serum creatinine 0.46 mg/dL). Hemoglobin concentration was mildly reduced (10.0 g/dL). Echocardiographic examination revealed diffusely impaired LV contraction (LVEF 15%), and cardiac catheterization indicated pulmonary congestion and extremely low cardiac output (pulmonary capillary wedge pressure 18 mmHg and cardiac index 1.21 L/minute/m²) without coronary artery stenosis. She was diagnosed as having cardiogenic shock due to anti-HER2 therapy-related cardiotoxicity, and BNP and troponin I reached the peak levels (2,698.4 pg/mL and 1,563.5 ng/L, respectively) thereafter (Figure 2). In addition to pharmacotherapy using diuretics and inotropic agents, venoarterial extracorporeal membrane oxygenation (VA-ECMO) with an Impella 2.5 device (Abiomed Inc., Danvers, MA, USA) was employed for 7 weeks to achieve hemodynamic stabilization in the management of cardiogenic shock. Consequently, her general condition gradually recovered. Cardioprotective application of the β-blocker bisoprolol, angiotensin-converting enzyme inhibitor enalapril, and mineralocorticoid receptor antagonist spironolactone was initiated and titrated. Ivabradine was administered for the management of inappropriate sinus tachycardia (Figure 2).

Six months after the diagnosis, her cardiac function had recovered from LVEF of 15% to 34% on echocardiographic examination, which was accompanied by substantial improvement of the BNP (105 pg/dL) and troponin I (< 10.0 ng/L) levels (Figure 2). Serial changes in the echocardiographic parameters of the patient are summarized in Table. She also underwent CMR at 3.0 T (Philips Achieva TX, USA) to evaluate cardiac function and myocardial damage before discharge. Cine CMR imaging demonstrated LV dysfunction (LVEF 27%), especially with akinetic motion in the mid-anteroseptal and apical-lateral wall, and apex (Figure 3). In contrast-enhanced T1-weighted imaging, transmural LGE was detected in the areas corresponding to these akinetic segments (Figure 3A, B), and the %LGE volume was calculated as 33.1% (100 x total LGE volume divided by total LV mass). CMR parametric mapping demonstrated that the global native T1 value and extracellular volume (ECV) in LGE-negative segments were elevated (global native T1 value 1309 msec; normal myocardium 1250 msec, MOLLI Philips 3.0T, ECV 39.2%; normal myocardium 29%) (Figure 4A). The T2-weighted image did not show
Figure 1. Electrocardiogram and chest x-ray image of the patient on admission. The electrocardiogram showed no significant abnormality, except for sinus tachycardia (111 beats/minute) (A), and the chest x-ray revealed severe congestion in bilateral lungs (B).

Figure 2. Time course of LVEF, BNP, and troponin I, and treatment of the patient. The β-blocker bisoprolol was started at a low dose of 1.25 mg twice a day and increased gradually up to 5 mg twice a day. The angiotensin-converting enzyme inhibitor enalapril was administered at 0.625 mg twice a day. The mineralocorticoid receptor antagonist spironolactone was initiated at 12.5 mg twice a day and increased up to 25 mg twice a day. Ivabradine was administered at 2.5 mg twice a day and increased up to 7.5 mg twice a day. AC indicates anthracyclines plus cyclophosphamide regimen; ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction; HER2, human epidermal growth factor receptor 2; IVA, ivabradine; MRA, mineralocorticoid receptor antagonist; and VA-ECMO, venoarterial extracorporeal membrane oxygenation.

apparently elevated signal intensity in LV myocardium, but the global native T2 value was also diffusely elevated (53.5 msec; normal myocardium 48 msec) (Figure 4B). These results suggest that myocardial damage was pronounced and widespread even in LGE-negative regions, and also indicate the existence of residual edema in the LV wall even more than 6 months after the onset of heart failure. Eventually, she was discharged from our hospital in a good clinical state.
Figure 3. Cine imaging and contrast-enhanced T1-weighted imaging 6 months after the onset of heart failure. A: Short-axis view of mid left ventricle (LV) (upper panels) and apical LV (middle panels), and 4-chamber view (lower panels) of cine imaging in diastole and systole. B: Short-axis view of mid LV (upper panel) and apical LV (middle panel), and 4-chamber view (lower panel) of contrast-enhanced T1-weighted imaging. Red arrowheads (B) indicate transmural late gadolinium enhancements (LGEs) in mid-anteroseptal and apical-lateral wall, and apex of LV myocardium, which correspond to the areas with akinetic motion in cine imaging (yellow dotted lines, A). The overall %LGE volume was 33.1% (total LGE volume divided by total LV mass × 100). LGE indicates late gadolinium enhancement.

Discussion

The patient developed fatal CTRCD following dual anti-HER2 therapy with trastuzumab and pertuzumab. After intensive and cardio-protective therapies, she recovered from cardiogenic shock, but her LV function was not fully restored. She did not have baseline cardiovascular risk factors other than the previous use of anthracyclines. Although low baseline LVEF or greater LVEF decline after anthracycline treatment were reported to be independent predictors of trastuzumab-induced CTRCD,14) LVEF after an AC regimen was preserved in this patient, and the cumulative dose of doxorubicin was moderate (240 mg/m²). It seems that the incidence of CTRCD is high when trastuzumab was administered concurrently or shortly after anthracyclines.15) Along with avoidance of the use of anthracyclines and trastuzumab concurrently or at short intervals, anti-HER2 therapy-related CTRCD becomes less frequent. However, there are a certain number of patients developing severe CTRCD following anti-HER2 therapy.

The important point in this patient is that fulminant cardiotoxicity occurred during the trastuzumab-pertuzumab combination therapy, and that LGE imaging and CMR parametric mapping revealed widespread myocardial damage and edema even more than 6 months after the onset of heart failure. Several studies reported that elevated native T1 and ECV in CMR were the typical findings in anthracyclines-treated patients,13,16) while LGE was not observed after low to moderate dose anthracycline treatment.17) In contrast, subepicardial linear LGE in the
lateral wall of the LV was frequently observed in patients with CTRCD after treatment with anthracyclines plus trastuzumab. The LGE-positive areas in this patient extended throughout the layers in multiple segments of the LV wall, which were apparently more extensive than those observed in most patients with trastuzumab-related cardiac dysfunction. Furthermore, the global native T1, ECV, and native T2 values were also significantly elevated, indicating diffuse myocardial fibrosis and persistent myocardial edema. Considering the severe clinical course of this patient, we propose that LGE imaging and parametric mapping by CMR are useful to assess the severity of anti-HER2 therapy-related cardiac dysfunction. CMR was not performed in the early phase in this patient, and further accumulation of cases is needed to determine the usefulness of CMR for the prediction of severity and reversibility of myocardial injury in patients receiving anti-HER2 therapy.

There has been an increase in the opportunity to use multi-parametric CMR in the field of cardio-oncology not only for baseline and serial assessment of cardiac structure and function but also for myocardial tissue characterization. The use of CMR also provides a significant value for the diagnosis of immune checkpoint inhibitors-related myocarditis, although the absence of LGE or abnormal native T1 or T2 values in patients with a clinical suspicion cannot exclude the diagnosis of myocarditis. Echocardiography continues to be the primary imaging modality, but its performance for the detection of subclinical CTRCD is inferior to that of CMR. The choice of imaging modality in clinical practice is generally determined on the basis of availability and cost. Comprehensive and serial studies by CMR including cost-benefit analysis will be required to rationalize the application of CMR for the detection and assessment of CTRCD in an individual patient who is treated with anthracyclines, anti-HER2 therapy, and other anticancer drugs with potential cardiotoxicity.

**Conclusion**

LGE with CMR parametric mapping might be applicable to evaluate not only the etiology of the underlying disease, but also the clinical severity of anti-HER2
therapy-related cardiac dysfunction, and ultimately the prognosis of cancer patients with CTRCD.

Disclosure

Conflicts of interest: The authors have no conflict of interest to declare.

References

1. Cote GM, Sawyer DB, Chabner BA. ERBB2 inhibition and heart failure. N Engl J Med 2012; 367: 2150-3.
2. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol 2015; 12: 547-58.
3. Florido R, Smith KL, Cuono KK, et al. Cardiotoxicity from human epidermal growth factor receptor-2 (HER2) targeted therapies. J Am Heart Assoc 2017; 6: e006915.
4. Kadowaki H, Akazawa H, Ishida J, et al. Cancer Therapeutics-related cardiac dysfunction- Insights from bench and bedside of onco-cardiology. Circ J 2020; 84: 1446-53.
5. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab for metastatic breast cancer. N Engl J Med 2012; 366: 109-19.
6. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012; 366: 109-19.
7. Harries I, Liang K, Williams M, et al. Magnetic resonance imaging to detect cardiovascular effects of cancer therapy: JACC CardioOncology State-of-the-Art Review. JACC CardioOncol 2020; 2: 270-92.
8. Harries I, Liang K, Williams M, et al. Magnetic resonance imaging to detect cardiovascular effects of cancer therapy: JACC CardioOncology State-of-the-Art Review. JACC CardioOncol 2020; 2: 270-92.