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HOW TO

How to Follow, Manage and Treat Cardiac Dysfunction in Patients With Her2+ Breast Cancer

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While known to increase the risk of cardiotoxicity, particularly left ventricular (LV) dysfunction and/or heart failure (HF), the use of trastuzumab for HER2+ breast cancer has been the standard of care since the 2000s (1). In adjuvant breast cancer trials, the overall reported incidence of symptomatic HF has been 2.5%, while asymptomatic declines in left ventricular ejection fraction (LVEF) occur more commonly (1). The Food and Drug Administration prescription label for trastuzumab (2) recommends baseline and surveillance LVEF measurements every 3 months during treatment, with scans every 6 months for at least 2 years following treatment completion, and holding/stopping therapy for LVEF decline to below normal and >10% absolute LVEF decrease from pretreatment values. However, compliance with imaging has varied, and concerns have been raised that interrupting or stopping trastuzumab early, due to declines in LVEF, can adversely influence cancer-related outcomes (3). The existing recommendations have been largely informed by the evidence of high cardiotoxicity risk with anthracycline and trastuzumab combination therapy in patients with metastatic disease and the subsequent design of adjuvant trastuzumab trials that incorporated frequent LVEF assessment (2). Extrapolation, however, may be misleading, given differing pathophysiology and limited long-term data with non-anthracycline HER2 therapy. As a result, balancing the (dis)continuation of trastuzumab-based therapy with cardiac risk remains a challenge, particularly as the recommendations do not account for the aggressiveness of the cancer and/or additional cardiovascular risks. Collaboration with the patient, oncologist, cardiologist, and multidisciplinary care team is required across the spectrum of care from diagnosis through cancer treatment and survivorship.

This paper presents clinical scenarios that illustrate challenges and practical solutions in the prevention, treatment and follow-up of cardiac dysfunction in patients with HER2+ breast cancer.

CASE 1. *A 55-year-old postmenopausal woman with no known preexisting cardiovascular (CV) risk factors is diagnosed with a stage I HER2+ breast cancer. With no high-risk tumor features (node negative, small tumor) her oncologist recommends paclitaxel weekly for 12 weeks with trastuzumab every 3 weeks for 12 months.*

The planned cancer treatment is considered low risk for cardiac dysfunction, with no anthracycline chemotherapy and a single HER2-targeted agent. The patient herself is also categorized as low risk given absence of CV risk factors. She should undergo standard baseline CV assessment, including history and examination, blood pressure (BP) measurement, and lipid panel (**Table 1**). All patients initiating HER2-targeted therapies should receive baseline LVEF assessment, ideally using echocardiography incorporating 3-dimensional LVEF and global longitudinal strain (GLS). For follow-up imaging, current Food and Drug Administration (2) and the American Society of Echocardiography/European Association of

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TABLE 1 Proposed Framework for Cardiology and Oncologic Risk Stratification for Cardiac Monitoring With Trastuzumab-Based Therapies in HER2-Positive Breast Cancer

Oncology Risk Group	Early Disease				Metastatic Disease	
	Low		Intermediate/High			
CV Risk Group	Low	Intermediate/High	Low	Intermediate/High	Low/Intermediate	Intermediate/High
First-line treatment options*	TH	TH	ACTHP, TCHP, TCH	ACTHP,† TCHP, TCH	THP	THP, TH
Treat modifiable risk factors	x	x	x	x	x	x
Refer to cardio-oncology/cardiology		x		x		x
Baseline echocardiography	x	x	x	x	x	x
3 monthly echocardiograms	x‡	x	x	x	x§	x§
Blood biomarkers (troponin, NT-proBNP)		x		x		x
Cardioprotection		x		x		x
Echo 6 to 12 months post-completion	x	x	x	x	NA	NA

Low CV risk: 0 or 1 CV risk factors. Intermediate/high CV risk: presence of >2 CV risk factors, presence of cardiac dysfunction, significant valvular disease, or other. *First-line oncology treatment options will continue to evolve based on new trial results and should be discussed with oncologist. †ACTHP in this situation could be considered with cardiology input. ‡Reasonable to reduce frequency of echocardiograms. §Consider reduced frequency if stable for 12 months.

ACTHP = doxorubicin, cyclophosphamide, paclitaxel, trastuzumab, pertuzumab; CV = cardiovascular; NA = not applicable; NT-proBNP = N-terminal pro-brain natriuretic peptide; TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab; TH = paclitaxel (Taxol) and trastuzumab (Herceptin); THP = docetaxel or paclitaxel, trastuzumab, pertuzumab.

Cardiovascular Imaging (4) statements recommend 3-monthly LVEF measurements during treatment and 6-monthly assessment for 2 years in survivorship. In contrast, the American Society of Clinical Oncology guidelines indicate that imaging frequency should be "determined by providers based on clinical judgment and patient circumstances" (5). The discrepancy between the documents may reflect significant difference in publication date (~15 years) with a growing evidence that CV and cancer factors may modulate cardiotoxicity risk.

Our patient, without CV risk factors and receiving taxane-trastuzumab therapy, has a low risk of symptomatic HF (0.4%) and we believe that it is reasonable to use provider judgment to personalize imaging frequency (6). In contrast, in a patient with CV risk factors, and/or abnormal baseline imaging, serial LVEF measurements would be indicated (2,5). Preventive strategies are unlikely to provide significant benefit in this context, and there is little evidence for routine serial blood biomarker surveillance. In the survivorship period, monitoring CV risk factors continues to be of importance given CV risk remains elevated in survivors even 7+ years after diagnosis.

CASE 2. *A 37-year-old woman with a history of Hodgkin lymphoma treated with ABVD chemotherapy (Adriamycin cumulative dosing 300 mg/m², bleomycin, vinblastine, and dacarbazine) and mantle radiation at age 19 years, presents with a stage IIB HER2+ breast cancer. Neoadjuvant chemotherapy with a non-anthracycline-based regimen with trastuzumab and pertuzumab is recommended.*

This is a patient at high risk for breast cancer recurrence and high risk for cardiac dysfunction. CV risk factors include prior history of high-dose mantle-field radiation therapy and anthracycline regimen with now planned HER2-targeted therapy. A comprehensive CV assessment and baseline echocardiography with 3-dimensional and GLS are recommended before treatment initiation. Baseline troponin can be considered as part of risk stratification, as prior studies showed high negative predictive value of combined GLS and troponin when normal (7).

Although the role of biomarkers such as N-terminal pro-brain natriuretic peptide (NT-proBNP) remain to be clarified, assessment before treatment initiation may be important to establish baseline risk and in the assessment of change over time.

Considerations of primary preventive strategies will vary based on the oncology therapy choice and cardiovascular risk profile. From the oncology perspective, this patient is likely to benefit from chemotherapy with combined HER2 therapy (such as docetaxel, carboplatin, trastuzumab and pertuzumab [TCHP]) followed by 1 year of trastuzumab and pertuzumab (HP) given every 3 weeks. Anthracycline-based regimens (such as doxorubicin, cyclophosphamide, docetaxel, trastuzumab, pertuzumab [ACTHP]) would bring this patient's cumulative doxorubicin dose to 540 mg/m², and should be avoided if possible. In patients with high risk of cancer recurrence for whom ACTHP is recommended, dexrazoxane cardioprotection should be considered before doxorubicin (5).

Primary cardiac preventive strategies that have been recently investigated during HER2-targeted therapy include beta-blockers (metoprolol, bisoprolol, and carvedilol), angiotensin-converting enzyme (ACE) inhibitors (lisinopril, perindopril, enalapril), angiotensin receptor blockers (ARBs) (candesartan) and statins. Overall, the studies showed good safety and feasibility but mixed and modest effect sizes (8). In this patient, a cardiology referral would facilitate the choice and titration of cardiac therapy based on presence of CV risk factors (e.g., hypertension, diabetes, cholesterol) and individual BP and heart rate values. Although there are no evidence-based data to support different recommendations for goal levels of BP or cholesterol in these patients, comprehensive CV screening and aggressive management are recommended in this patient based on high CV risk (e.g., BP <130/80 mm Hg, optimal diet, weight, and exercise) (5). Low-density lipoprotein goal based on atherosclerotic cardiovascular disease risk should be calculated with individual decision acknowledging absence of mediastinal radiation history in that model.

CASE 2 CONTINUED. *The patient completes TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab) and undergoes surgery. She has a complete response to neoadjuvant chemotherapy. Cancer treatment with 1 year of postoperative trastuzumab and pertuzumab (HP) is recommended. Follow-up echocardiogram after the first cycle of HP monotherapy demonstrates an LVEF of 44%.*

Decline in LVEF with TCHP is most suggestive of cardiotoxicity related to HER2 therapy, particularly in the setting of prior anthracycline exposure. However, even here it is important to exclude other causes of cardiomyopathy, including ischemia (of which the risk is increased given prior mantle radiation), metabolic, infective, or inflammatory processes. In a patient with a new LVEF decline, NT-proBNP is obtained as part of a HF evaluation and assessment of interval change from baseline may aid in risk stratification. Patients with asymptomatic LV dysfunction need to be referred to a cardiologist with expertise in cardio-oncology and started on HF medications as soon as possible. In absence of clinical HF symptoms, early continuation of oncologic therapy can be considered concomitantly with administration of cardiac medications and close cardiotoxicity surveillance. This is based on recently completed, small trials indicating safety of HER2 agents in patients with mildly reduced LVEF who were treated with HF medications and followed by cardiology (9,10). In the SAFE-HEaRt trial, carvedilol and ACE-inhibitor or ARB were titrated rapidly and timeline for (re)-initiation of HER2 targeted therapy was <21 days from enrollment (9). Close communication between the oncologist and cardiologist is critical to address the following questions: 1) continuation of trastuzumab-pertuzumab (HP) versus trastuzumab (H) alone; 2) time of reinitiation and duration of planned oncology therapy; and 3) continued cardiac therapy and frequency of LVEF and biomarker assessment. Reassessment of LVEF and NT-proBNP within 3 to 4 weeks of LVEF decline and continued cardiovascular and oncology treatment in patients who remain asymptomatic with an LVEF that improves or stays mildly reduced is recommended. In the adjuvant setting, continuing trastuzumab alone instead of a dual HER2 regimen can be considered based on the individual benefit-risk ratio. Although clinical trials showed no evidence of greater cardiotoxicity in the trastuzumab-pertuzumab arms, these observations cannot be readily applied to patients with LVEF decline who would have been excluded or had treatment held based on cardiac function changes. Frequency of further cardiac evaluation may be later reduced in stable patients (e.g., at 6 weeks, then every 3 months in the SAFE-HEaRt study) (9); however, patients with symptoms or further decline in LVEF need individual discussion about relative breast cancer and HF risk.

CASE 2 CONTINUED. *Patient completes 1 year of trastuzumab (based on the oncologist's preference and the complete pathological response after neoadjuvant therapy, only trastuzumab was continued). LVEF at treatment completion is 55%.*

There are limited data on the optimal duration of neurohormonal therapy and cardioprotective medications in patients with cardiotoxicity, or the frequency and duration of LVEF surveillance after treatment completion. It is reasonable to continue cardiac medications for at least 6 months posttreatment followed by an individual discussion and consideration of concomitant comorbidities, CV risk factors, patient preference, level of physical activity, and medication tolerance. Women who desire pregnancy should be evaluated by cardiologists early (preconception) to reevaluate risk and benefit of cardiac medications. Statins and renin angiotensin inhibitors need to be stopped before attempting pregnancy and plan for CV management needs to include the obstetrics team.

CASE 3. *A 68-year-old woman with hypertension and diabetes who had undergone percutaneous intervention (PCI) following a non-ST-segment elevation myocardial infarction 3 years prior, is diagnosed with Stage IV metastatic HER2+ breast cancer. She has a good performance status with no HF symptoms despite a baseline LVEF of 48%.*

This patient is at high risk of cardiotoxicity given her preexisting CV disease and mildly impaired LV function, and therefore a careful balance of potential risks and benefits of any proposed cardiotoxic cancer treatment should be undertaken. Early referral for specialist assessment with on-going management decisions taken in a multidisciplinary setting is recommended.

She has metastatic HER2-positive disease for which first-line therapy is THP (docetaxel, trastuzumab, and pertuzumab) administered every 3 weeks for 6 cycles, with subsequent dual HER2 therapy until disease progression. HER2 targeted therapies offer significant incremental benefit over chemotherapy alone (1), with recent evidence supporting dual HER2 therapy over single-agent trastuzumab in the metastatic setting (56.5 vs. 40.8 months median overall survival). Patients with metastatic HER2-positive breast cancer can live for many years (median survival 60 months). Given both the potential for significant clinical benefit from HER2 therapy with few effective alternatives, and the reduced relevance of late cardiotoxicity in this context compared with early breast cancer, the threshold for interrupting HER2 therapies may be higher.

Before treatment initiation, risk factors should be aggressively treated (in this case with antiplatelet agents, high-dose statin therapy, target systolic BP <130 mm Hg, healthy exercise, and diet). The administration of HER2 therapies can be achieved at relatively low risk in asymptomatic patients with mild cardiac dysfunction (LVEF 40% to 49%) provided they are closely monitored (9,10). Although data are limited, consensus recommendations suggest a role for cardioprotection with ACE inhibitors, ARBs, and/or beta-blockers (5). In addition to continued cardiac imaging, monitoring of blood biomarkers (NT-proBNP, troponin) may be beneficial in individuals with cardiac dysfunction who are continuing HER2 therapies, to assist with risk stratification and diagnosis of symptomatic HF.

During treatment with HER2 therapies, patients with metastatic disease should initially undergo recommended 3-monthly serial imaging initially. If LVEF is stable for 12 months and the patient remains asymptomatic, the frequency can potentially be reduced to 6 monthly intervals, particularly if biomarkers remain stable. This decision should be individualized. Any symptoms of HF warrant urgent reassessment and a low threshold for holding treatment. Any decision to interrupt or terminate HER2 treatment should be made after discussion between oncology and cardiology, with close involvement of the patient.

Data for the cardiotoxicity of second- and third-line treatments in metastatic HER2-positive breast cancer (including trastuzumab conjugates such as trastuzumab emtansine, trastuzumab deruxtecan, lapatinib, neratinib, and tucatinib) are limited, and screening should follow the principles used for first-line treatments until further data are available. Alternatives to HER2 therapies in patients with performance status >1 who are at very high CV risk or who develop cardiotoxicity include taxanes, capecitabine, and gemcitabine; serial cardiac monitoring is not required for these patients. However, most patients will continue on trastuzumab-based therapy with chemotherapy in the metastatic setting, in which case, monitoring should be continued in a risk-stratified approach.

AUTHOR DISCLOSURES

Dr. Barac has served as a consultant for Takeda Oncology. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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