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HOW TO

# How to Manage and Monitor Cardiac Dysfunction in Patients With Metastatic HER2-Positive Breast Cancer

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The introduction of human epidermal growth factor receptor 2 (HER2)-targeted therapies into clinical practice has led to significant improvements in clinical outcomes for women with early and metastatic HER2-positive breast cancer (BC). The risk for cardiotoxicity with HER2-targeted agents, which clinically presents as heart failure (2.5%-4%) or more commonly as asymptomatic declines in left ventricular ejection fraction (LVEF), has challenged clinicians to balance effective cancer therapy vs cardiotoxicity risk.[1] Our improved understanding of the potential cardiac consequences of these agents has led to the safer administration (eg, avoiding anthracyclines) of HER2-targeted therapies, particularly in early-stage BC, resulting in relatively lower rates of cardiotoxicity, but what about women with metastatic disease? Today, patients with metastatic HER2-positive BC are offered multiple lines of HER2-targeted therapy (single agent or in combination), resulting in median overall survival (OS) of approximately 5 years, with 30% to 40% alive at 8 years.[2] How do we balance the clinical efficacy of these drugs with the potential risk for cardiotoxicity, particularly given that patients may be treated with multiple lines of therapy? The U.S. Food and Drug Administration recommendations of LVEF monitoring every 3 months during treatment and every 6 months for at least 2 years following therapy completion and holding HER2 therapy for an LVEF decline of >10% to <50% are based on older trials in which anthracyclines were given in combination with trastuzumab. These recommendations were focused primarily on the treatment of early-stage BC and have not been updated to incorporate the use of newer HER2-targeted agents, particularly when given in the metastatic setting. In this primer, we use a case to illustrate our approach to the treatment of HER2-positive metastatic BC in the setting of left ventricular dysfunction (LVD) and propose cardiac surveillance strategies.

## CLINICAL CASE

A 48-year-old premenopausal woman presented with de novo metastatic BC with liver and bone involvement. A liver biopsy demonstrated adenocarcinoma, consistent with breast primary, estrogen receptor 0%, progesterone receptor 0%, HER2-positive (immunohistochemistry 2+), and fluorescence in situ hybridization amplified. She had a history of hypertension treated with hydralazine and a body mass index of 32 kg/m$^2$. Echocardiography prior to cancer therapy demonstrated an LVEF of 50%, grade 1 diastolic dysfunction, global longitudinal strain (GLS) of −16%, and no significant valvular disease. She was asymptomatic. Her oncologist recommended systemic therapy with docetaxel, trastuzumab, and pertuzumab (**Figure 1**). Although this regimen is considered

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**HIGHLIGHTS**

- Targeted therapies improve clinical outcomes in HER2+ metastatic breast cancer.
- There is thus far minimal signal of increased risk of cardiotoxicity from novel HER2 targeted therapies.
- Cancer therapy benefit drives clinical decision-making with LV dysfunction.
- The frequency of cardiac monitoring should be based on a risk-benefit approach.

lower risk for LVD (no anthracyclines), the patient had clinical risk factors that placed her at greater cardiotoxicity risk.

## HOW TO ASSESS CARDIOVASCULAR RISK IN PATIENTS WITH CANCER RECEIVING CARDIOTOXIC CANCER THERAPY

Although oncologists generally consider the potential risk for cardiotoxicity with cancer therapies, such as anthracyclines and HER2-targeted agents, in making their treatment recommendations, less attention has been given to the impact of an individual's baseline cardiovascular (CV) risk factors or disease. Planning treatment with cancer agents with potential cardiotoxicity provides a unique opportunity to assess CV health before the initiation of treatment. A position statement from the Heart Failure Association of the European Society of Cardiology, in collaboration with the International Cardio-Oncology Society, includes practical tools to risk-stratify patients prior to cancer therapy.[3] A clinical risk algorithm for several classes of cancer drugs, including HER2-targeted agents, is calculated on the basis of medical CV risk factors, lifestyle, previous CV disease, previous cardiotoxic cancer treatment, and cardiac biomarkers (if available). Using the risk algorithm for HER2-targeted therapies, this patient would be considered to be at high risk. Patients considered at high risk should be referred for cardio-oncology assessment to optimize CV health (**Figure 1**).

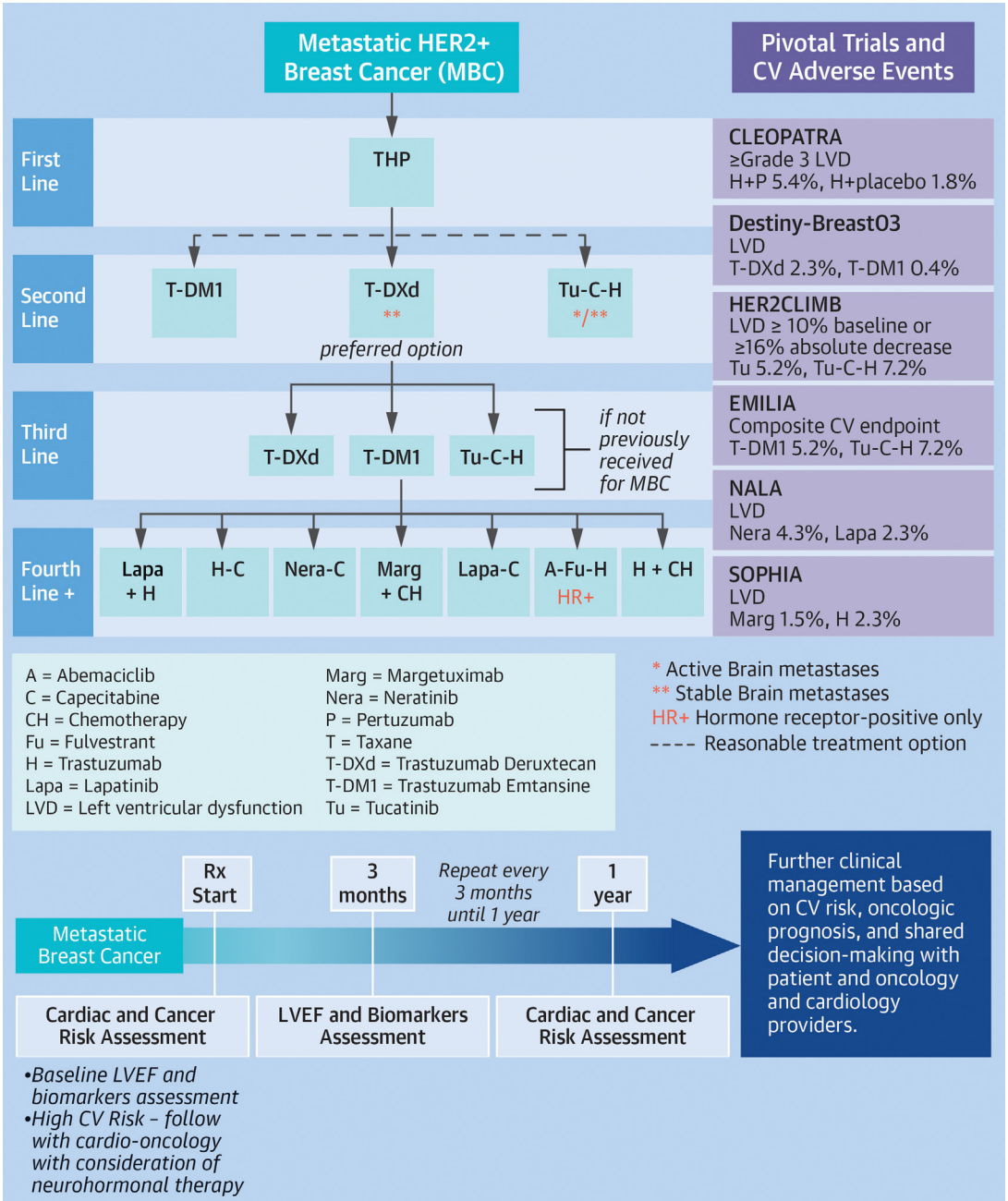
## CLINICAL CASE CONTINUED

The patient was seen in the cardio-oncology clinic, and on the basis of her high clinical CV risk, her antihypertensive regimen was changed to appropriate heart failure goal-directed medical therapy. She then started therapy with docetaxel, trastuzumab, and pertuzumab. Restaging scans (chest, abdominal, and pelvic computed tomography and bone scan) and repeat echocardiography at 3 months showed stable metastatic disease and stable LVEF of 46% (GLS −15.5%). Her blood pressure was well controlled, and brain natriuretic peptide (BNP) was 35 to 50 pg/mL throughout the course of her monitoring. A few months later, she developed increasing abdominal pain. Repeat imaging demonstrated significant progression of her liver disease. When her oncologist considered her next line of HER2-targeted therapy, the question arose whether one should be concerned that her left ventricular function might be negatively affected by switching to another treatment.

## HOW TO MANAGE HER2-POSITIVE METASTATIC BC

The recent approval of several new HER2-targeting agents in the metastatic setting has added to the complexity of decision making. Dual anti-HER2 therapy with pertuzumab/trastuzumab plus a taxane is considered the standard first-line therapy on the basis of the CLEOPATRA (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer) trial[4] (**Figure 1**) Ado-trastuzumab emtansine (T-DM1), an antibody-drug conjugate, has been considered the standard second-line treatment approach, demonstrating better progression-free survival (PFS) (9.6 vs 6.4 months) and OS (30.9 vs 25.1 months) in comparison with lapatinib/capecitabine.[1] Fam-trastuzumab deruxtecan (T-DXd) has recently demonstrated superiority over T-DM1 on the basis of the results of DESTINY-Breast03 (DS-8201a Versus T-DM1 for Human Epidermal Growth Factor Receptor 2 [HER2]-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane), with a significant improvement in PFS (25.1 vs 7.2 months) and a strong trend toward an OS benefit favoring the T-DXd arm, and hence is now considered preferred second-line treatment.[5] In HER2CLIMB (A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer), the addition of tucatinib to capecitabine and trastuzumab in the third-line setting resulted in improved PFS at 1 year (33.1% vs 12.3%) and OS at 2 years (44.9% vs 6.6%).[6] Margetuximab vs trastuzumab in heavily pretreated patients was investigated in the SOPHIA (Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of HER2+

**FIGURE 1 Treatment Options and Cardiovascular Events in Metastatic HER2-Positive Breast Cancer**




Recommendation for human epidermal growth factor receptor 2 (HER2)-targeted therapy for metastatic breast cancer alongside a list of 6 pivotal trials with observed cardiovascular adverse events with recommended cardiovascular monitoring guidelines on the basis of cardiovascular risk and cancer prognosis. CLEOPATRA = A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer; CV = cardiovascular; DESTINY-Breast03 = DS-8201a Versus T-DM1 for Human Epidermal Growth Factor Receptor 2 (HER2)-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane; EMILIA = A Study of Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-Positive Locally Advanced or Metastatic Breast Cancer; HER2CLIMB = A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer; LVEF = left ventricular ejection fraction; NALA = A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting; Rx = therapy; SOPHIA = Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer.

Metastatic Breast Cancer) trial; PFS was significantly longer with margetuximab in the intention-to-treat population (5.8 months vs 4.9 months), although the final analysis did not demonstrate a statistically significant OS advantage with margetuximab.[7]

Although the increased efficacy of newer anti-HER2 agents is encouraging, there are limited data on CV toxicities. Despite containing trastuzumab, thus far the reported rates of cardiotoxicity associated with T-DXd have been low and similar to other antibody-drug conjugates containing trastuzumab, such as T-DM1 (**Figure 1**). Decreases in LVEF were seen in 1.7% of patients receiving T-DM1 in the advanced setting; however, in these trials, patients were excluded if they had LVEFs <50%, so these low rates may not be reflective of patients treated in the non-clinical trial setting. Several other HER2-targeted therapies (neratinib, lapatinib, tucatinib, and margetuximab) have been shown to be efficacious in metastatic HER2 disease, with low rates of CV events.[1]

In the metastatic setting, the benefit of cancer therapy should drive clinical decision making, even in the presence of LVD. The results of the SAFE-HEaRt (Cardiac Safety Study in Patients With HER2+ Breast Cancer) trial demonstrated that the majority (90%) of the 30 evaluable patients with mild asymptomatic LVD (LVEF 40%-49%) receiving concomitant cardioprotective medication (beta-blockers and/or angiotensin-converting enzyme inhibitors) were able to complete their planned HER2-targeted therapy.[8]

## CLINICAL CASE CONTINUED

The patient was started on T-DXd and had stable disease for 8 months. She then developed intense headaches, which had increased in severity over the past few weeks. She was unsteady on her feet. Magnetic resonance imaging of the brain demonstrated innumerable cerebellar lesions consistent with brain metastases. Additional imaging showed progressive liver and bone metastases. She was treated with whole-brain radiation therapy. After radiation, she saw her medical oncologist to discuss systemic therapy options. She was also seen in the cardio-oncology clinic. She was asymptomatic, but her BNP was now 120 pg/mL, and her LVEF was 41%. She was referred to the advanced heart failure clinic, where she was counseled regarding treatment options, and goal-directed medical therapy for heart failure was further optimized.

## METASTATIC BC AND BRAIN METASTASES

Up to 50% of patients with metastatic HER2-positive BC will develop brain metastases during their disease course.[9] On average, the onset of HER2-positive brain metastases is 13.3 months from the initial diagnosis of metastatic disease. Localized therapies, including resection and radiation, are often the first treatment strategy. After localized therapy, systemic treatment is initiated or continued. Two drugs have shown outstanding efficacy in this population, tucatinib and T-DXd.

The HER2CLIMB trial was unique in that it enrolled a significant proportion (48%) of patients with brain metastases, including those previously untreated, treated and stable, and treated with progressive brain metastases.[6] Among patients with brain metastases, PFS was significantly improved with tucatinib vs placebo (7.6 months vs 5.4 months). Importantly, those patients who had isolated central nervous system progression while on tucatinib with stable extracranial disease were allowed to undergo radiation therapy and continue the study. In DESTINY-Breast03, patients with stable brain metastases treated with T-DXd experienced a 63.9% response rate in the brain, with 10 (27.8%) achieving a complete response.[5] Comparatively, those treated with T-DM1 had a 33.4% intracranial response rate, with only 1 (2.8%) complete response.

Both T-DXd and tucatinib, trastuzumab, and capecitabine (the HER2CLIMB regimen) can be used in the setting of brain metastases. At this time, the HER2CLIMB regimen has more data on patients with actively progressing brain metastases.[6]

## CLINICAL CASE CONTINUED

The patient was seen by cardio-oncology monthly for repeat LVEF estimation and BNP measurements. She started the HER2CLIMB regimen. She was seen by the pharmacist to ensure that there were no drug-drug interactions between tucatinib and her cardiac medications. At 2 months, her LVEF was 43%, GLS was −15.5%, and BNP was 68 pg/mL. Her repeat staging scans showed stable metastatic disease. She remained concerned about the impact of her cancer therapy on her heart function and asked her oncologist how frequently she should undergo echocardiography.

## HOW TO OPTIMIZE CARDIAC MONITORING IN PATIENTS WITH METASTATIC HER2-POSITIVE BC

Per Food and Drug Administration and imaging guidelines, patients with BC treated with HER2-targeted therapy should undergo LVEF monitoring every 3 months during therapy (1 year). However, there is less specific guidance on cardiac monitoring

in the metastatic setting. Current guidelines do not acknowledge underlying CV risk factors. In the proposed algorithm in **Figure 1**, using the European Society of Cardiology/International Cardio-Oncology Society risk stratification algorithm, we endorse that patients with HER2-positive BC, especially those identified with high CV clinical risk, should undergo echocardiography and cardiac biomarker assessment every 3 months for the first year.[1,10] Those considered at less than high risk should be evaluated clinically at least every 6 months up to year 2 and annually thereafter.

Cardiac surveillance beyond 1 year should be driven by assessing cardiac risk and cancer prognosis. Beyond 1 year, we suggest that biomarkers such as BNP be obtained with every cycle of HER2-targeted therapy. Elevations in BNP levels beyond the 99th percentile for age, or clinical worsening, can then be followed up with LVEF measurement.[10] Our rationale to this approach is to promote a strategy based upon risk-guided screening and prognosis-guided care and the overall most efficient and effective use of resources for the patient and health care system. Patients with a poor cancer prognosis (<1 year) should undergo CV investigations as clinically indicated, on the basis of shared patient decision making. In the absence of data, patients who switch HER2-targeted agents should follow the same principles as described previously with a risk-guided approach.

In summary, for patients with HER2-positive metastatic BC, we propose that the benefit of uninterrupted cancer therapy should drive clinical decision making even in the presence of LVD. The frequency of cardiac monitoring should be based on a risk-benefit approach.

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