



Case Report

Cardio-Oncology Risk Assessment and Management in Patients Receiving Pertuzumab and Trastuzumab: Case Report and Literature Review

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Abstract

Pertuzumab significantly improved the rates of invasive-disease-free survival among patients with HER2-positive, operable breast cancer when it was added to trastuzumab chemotherapy. Pertuzumab is a HER2/neu receptor antagonist is indicated by Food and Drug Administration for: 1) Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease; or 2) Use in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer. Pertuzumab use can be associated with cardiac-related adverse events, including CHF and decline in LVEF. Patients should be screened into low and high-risk categories. Prior to initiating this combination therapy, a detailed clinical history of cardiovascular risk factors is indicated along with protocol-driven periodic TTE monitoring during therapy.

Keywords: Breast cancer; Cardio-Oncology; Cancer treatment-related cardiac dysfunction; Left ventricular ejection fraction; Pertuzumab; Trastuzumab

Abbreviations: MBC: Metastatic Breast Cancer; DM: Diabetes Mellitus; HTN: Hypertension; HLD: Hyperlipidemia; CHF: Congestive Heart Failure; PR: Progesterone Receptor; ER: Estrogen Receptor; TTE: Trans-Thoracic Echocardiogram; LV: Left Ventricle; RV: Right Ventricle; LVEF: Left Ventricular Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection

Fraction; PASP: Pulmonary Artery Systolic Pressure; mmHg: Millimeters of Mercury; TCHP: Taxotere, Carboplatin, Herceptin, and Pertuzumab; GLS: Global Longitudinal Strain; MR: Mitral Regurgitation; TR: Tricuspid Regurgitation; 2D: Two Dimensional; 3D: Three Dimensional; CO: Cardio-Oncology; HR: Heart Rate; bpm: Beats Per Minute; BP: Blood Pressure; Trop: Troponin; ng/mL: Nanograms per Milliliter; NT-ProBNP: N-Terminal-Pro hormone B-type Natriuretic Peptide; pg/ml: Picograms Per Milliliter; TSH: Thyroid Stimulating Hormone; mU/l: Milliunits Per Liter; GDMT: Guideline Directed Cardio-Medical Therapy;

CTLCD: Cancer Treatment-Related Cardiac Dysfunction; CCTA: Coronary Computed Tomography Angiography; mmol/L: Millimoles Per Liter; mg: Milligrams; PO: By Mouth; BID: Twice Daily; QOL: Quality-of-Life; SGLT2: Sodium-Glucose Transport Protein 2; NYHA: New York Heart Association; MRA: Mineralocorticoid Receptor Antagonist

Case Presentation

A 62-year-old female with past medical history of type II DM on metformin, HTN on amlodipine, and HLD on diet management, was diagnosed with a recurrence of ER positive, PR negative, HER-2 positive stage II A, right-sided breast cancer in May of 2020. Magnetic resonance imaging of the breast showed that the mass measured 2.4 centimeters in diameter. Her past oncological related history is significant for an ER positive HER-2 and PR negative breast cancer diagnosed in 2003. She then underwent right side lumpectomy with eighteen lymph nodes removed that same year. She also received adriamycin (dose not available), cytoxan, and taxol based chemotherapy, followed by radiotherapy and anastrozole for five years until 2009.

Her workup included a baseline TTE in June of 2020 which revealed a LVEF of 50-55%, grade I LV diastolic

dysfunction, normal right ventricle size and systolic function, no hemodynamically significant valvular abnormalities or pericardial effusion, and an estimated PASP of 23 mmHg.

Her second TTE in October of 2020 after five cycles of trastuzumab and pertuzumab revealed a LVEF 45-50%. The left ventricular global function was mildly reduced with global hypokinesis and grade I LV diastolic dysfunction. Normal right ventricular size and function was present. There was no significant valve dysfunction. Trastuzumab and pertuzumab were held for the first time. A follow up TTE three weeks later showed an LVEF 50-55%, improved from 45-50%, as noted on her second TTE. Trastuzumab and pertuzumab were then restarted. After receiving a total of six cycles of neoadjuvant TCHP therapy, the patient underwent a bilateral mastectomy in December of 2020. Following the surgery, the patient received two more cycles of TCHP.

Her three-month follow-up TTE in January of 2021 revealed an LVEF 20 to 25% by 2D imaging and 25% by 3D imaging, a mildly dilated LV with severely reduced function, and normal RV size with a moderately reduced function. GLS was reduced at -4.2 %, (Figure 1) with mild MR and moderate TR.

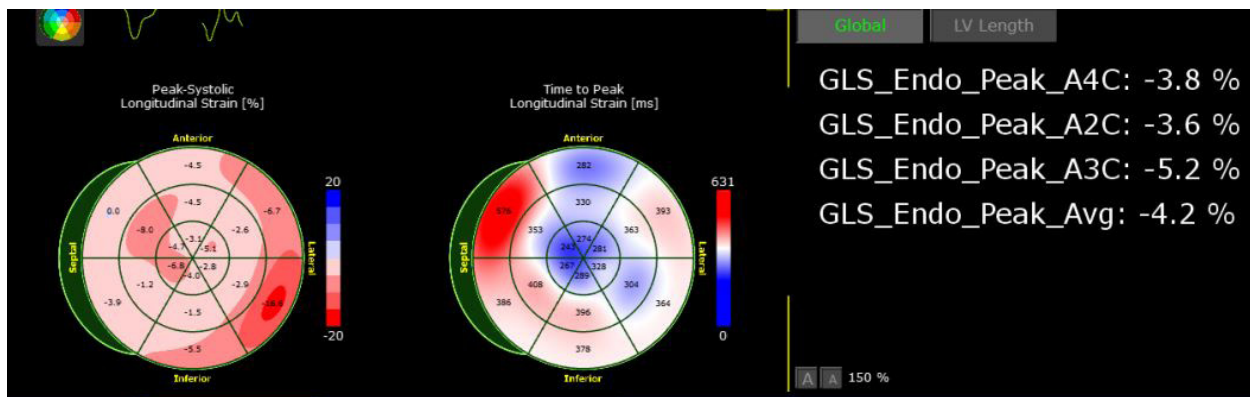


Figure 1: TTE shows a severely reduced GLS of -4.2%.

A CO consultation was obtained by the oncology service. Trastuzumab and pertuzumab were held for the second consecutive time during her treatment course. The patient reported shortness of breath with mild exertion with no associated chest pain. Her vitals at the initial CO consultation office visit revealed a HR of 111 bpm and a BP of 113/85 mmHg.

Her Trop-I revealed a value of -0.03 ng/mL, her NT-ProBNP level was elevated at 3,113 pg/ml, and her TSH level was normal at 3.76 mU/l. The patient was initiated on GDMT with carvedilol, sacubitril-valsartan, and atorvastatin, due to CTRCD as her LVEF had dropped by approximately 10% to now less than 53%.

Given her borderline low blood pressure, the amlodipine was discontinued to allow treatment with GDMT for her new LVEF decline and furosemide was initiated for diuresis. Metformin was continued for her type II DM.

CCTA performed to evaluate for ischemic cardiomyopathy revealed a coronary calcium score of zero and no coronary artery disease was noted. Through the CCTA it was noted that she had a RV enlargement with multiple filling defects involving the right ventricular apex and a small filling defect involving a left lower lobe pulmonary arterial lower lobe branch compatible with a pulmonary embolus; therefore, apixaban was added to her medical regimen.

After one week of GDMT her NT-ProBNP decreased to 2,364 pg/ml. Her HR was 99 bpm and BP was 96/72 mmHg. Her shortness of breath with exertion significantly improved from the prior visit. At her three-week follow-up her BP was 103/75 mmHg and HR was 103 bpm. Ivabradine 5 mg PO BID was added to her regimen. The patient lost close to ten pounds with good diuresis and GDMT. Her lower extremity edema resolved. She was referred to advanced CHF services. As far patient received cycle 8 of 18 scheduled cycles of TCHP. She was started on letrozole by the oncology services.

Approximately ten weeks into GDMT and post-cessation of trastuzumab and pertuzumab based chemotherapy, her TTE on showed a LV GLS of -12% (Figure 2). Her LVEF was 28% by 2D Simpson`s quantitative assessment with contrast.

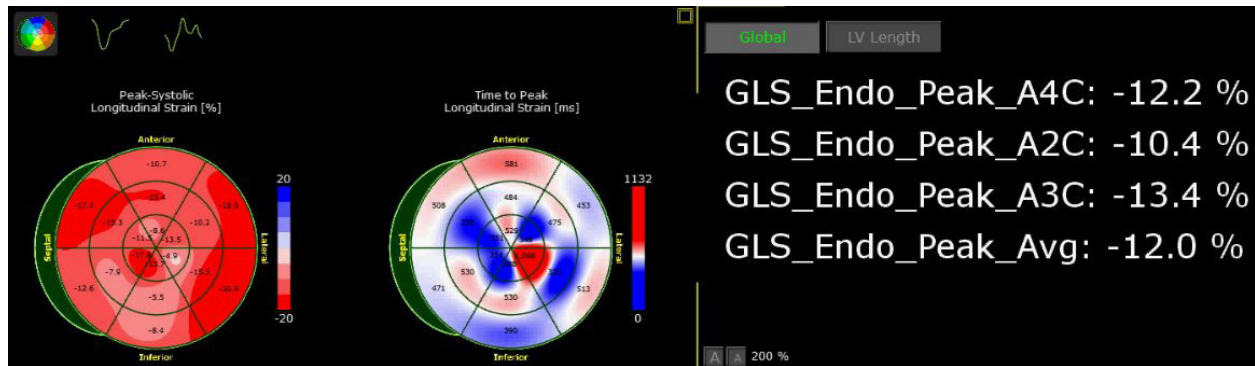


Figure 2: TTE at 10 weeks after holding trastuzumab and pertuzumab as well as on GDMT her severely reduced GLS improved to -12%.

In April of 2021, her carvedilol was increased to 6.25 mg BID and two medications were added to her regimen- Dapagliflozin 10 mg and Aldactone 25 mg PO daily. With the stabilization of her CHF manifestations, the oncology services initiated her on extended adjuvant therapy with Neratinib in May of 2021. Approximately seven months post HP treatment hold and with GDMT, the patient had a repeat TTE which was compared to the TTE performed upon cessation of her HP treatment and before initiation of the GDMT. There was a significant improvement in her LVEF to 45% and GLS to -17% (Figure 3).

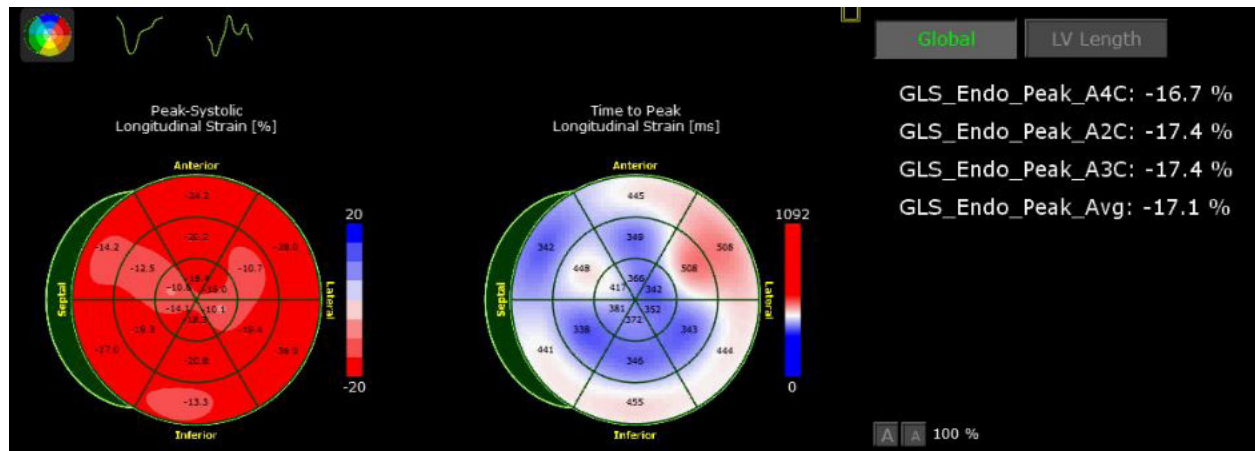


Figure 3: TTE 7 months post holding HP treatment and on GDMT, her LV GLS improved from -12% to -17%.

At her most recent follow-up, the patient reported decreased shortness of breath with exertion, resolved lower extremity edema, and was more functional with her activities of daily living.

Discussion

Pertuzumab is a HER2/Neu receptor antagonist indicated for: a) Use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease, b) in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than two cm in diameter or node positive) as part of a complete treatment regimen for early breast cancer [1]. These indications are based on the APHINITY trial which demonstrated a significant improvement in the invasive-disease-free survival among patients with HER2-positive, early breast cancer when it was added to trastuzumab and chemotherapy among patients with HER2-positive early breast cancer [2].

Gianni, et al. in the NeoSphere trial [3], demonstrated a higher five year progression-free survival rate among patients receiving only twelve weeks of pertuzumab in combination with trastuzumab compared to among patients receiving trastuzumab alone (hazard ratio for progression or death, 0.69; 95% CI, 0.34 to 1.40). The addition of pertuzumab to trastuzumab-docetaxel neoadjuvant treatment for twelve weeks in this randomized, multicenter, open-label trial resulted in a significant increase in the pathological complete response rate, from 29.0% to 45.8%. The full prescribing information for -pertuzumab has a warning in reference to LV dysfunction. Subclinical and clinical cardiac failure would manifest as decreased LVEF and CHF. The prescribing information suggests evaluating cardiac function prior to and during treatment with pertuzumab and discontinuing pertuzumab for a confirmed clinically significant decrease in LVEF. The Neosphere trial showed a LVEF decline greater than 10% and a LVEF drop to less than 50% in 2% of patients treated with neoadjuvant trastuzumab and docetaxel compared to 8% of patients treated with neoadjuvant pertuzumab in combination with

the trastuzumab and docetaxel [3]. In patients receiving adjuvant pertuzumab in the APHINITY trial, the incidence of NYHA Class III/IV CHF with a LVEF decline of greater than or equal to 10% and a drop to less than 50% was seen in 0.6% of pertuzumab treated patients compared to 0.2% of placebo treated patients. Most of the events (86%) occurred in patients treated previously with anthracycline-based chemotherapy, such as our patient.

Our case highlights the need for a protocol driven CO evaluation prior to initiation of trastuzumab-pertuzumab with detailed assessment of the patient's clinical history, specifically looking at cardiovascular risk factors such as HTN, HLD, DM, history of CHF, valvular heart disease, and prior use of anthracycline based chemotherapy. Additionally, routine baseline assessment of LVEF with regular monitoring of LV function by TTE during treatment should be performed in patients with cardiac risk factors or those who develop relevant cardiac signs or symptoms. Patients with cancer therapy-related adverse events or comorbidities should also undergo periodic detailed cardiovascular assessment with risk factor modification measures including pharmacological intervention with GDMT and non-pharmacological intervention with the ABCDE (Awareness of risks of heart disease, Blood pressure and cholesterol management, tobacco Cessation, Diet and weight management, Diabetes preventive measures, Exercise and Echocardiogram) approach as detailed previously by Montazeri et al. [4].

We developed a CO protocol risk assessment algorithm for patients who will be started on HER-2 based targeted therapy at our institution based on two sets of previously published guidelines [5,6]. This protocol risk assessment algorithm will guide our oncologists when referring patients for detailed cardiovascular risk assessments and involves optimizing cardiac risk factors prior to initiation of chemotherapy to best provide CO support to high-risk patients such as the one mentioned in this case (Figure 4).

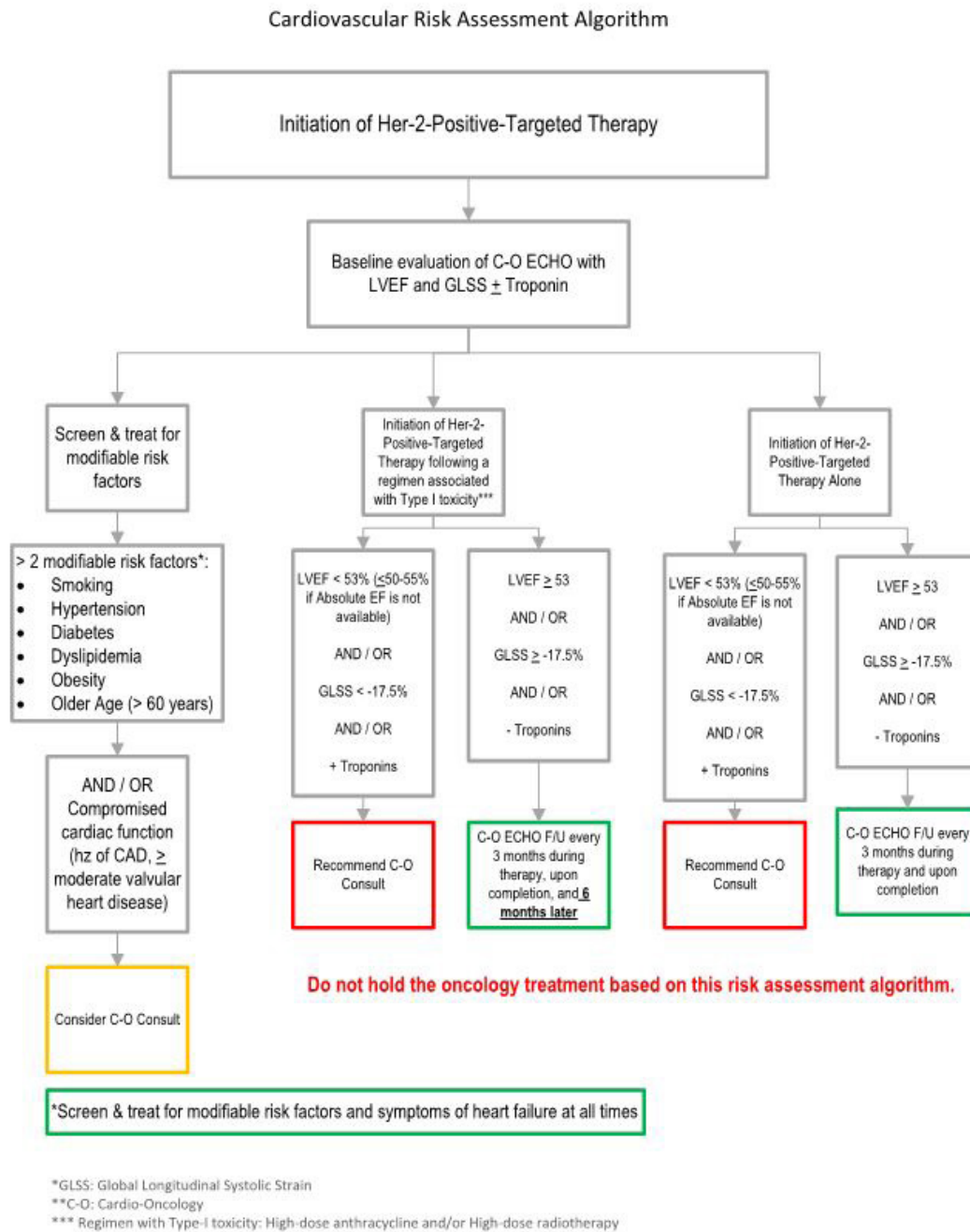


Figure 4: Cardiovascular risk assessment algorithm (Initiation of HER-2 positive targeted therapy).

Due to inability to utilize strain imaging technology until January of 2021, our institution was unable to track our patient’s LV GLS measurements until her echocardiography showed LV systolic dysfunction. However, we were able to track improvement in her LV GLS measurements with GDMT along with her LVEF through serial TTE monitoring. Our patient demonstrated an increase in her LV GLS approximately three months into GDMT and cessation of trastuzumab-pertuzumab based chemotherapy. Her LV GLS increased to -12% and her recovery in LVEF followed four months later by the subsequent TTE showing LVEF improvement from 29% to 47%. LV GLS is noted to be the measure of deformation for early detection of sub-clinical LV dysfunction. Our patient with HFrEF received GDMT

as previously mentioned by McDonagh, et al. [7].

A heart failure approved beta-blocker such as carvedilol helps to modulate excessive adrenergic drive to therefore reduce mortality [8]. The combination of sacubitril and valsartan works by targeting the natriuretic peptide system, specifically by collectively inhibiting the degradation of neprilysin and the renin angiotensin axis [9]. Ivabradine was indicated for our patient due to her low EF of less than 40% in the setting of a HR above 70 bpm on the maximum tolerated dose of carvedilol [10]. GDMT combined with ivabradine has been shown in many studies to cause reversal of LV remodeling in HFrEF patients and leads to a meaningful improvement in QOL measures.

The SGLT2 inhibitor Dapagliflozin was indicated due to her low EF of less than 40%, high NT-proBNP of greater than 600 pg/ml, and NYHA class III CHF classification. SGLT2 inhibitors have been shown to reduce the risk of worsening CHF and cardiovascular death; however, the medication's mechanism of action has not yet been elucidated [11].

The MRA spironolactone has been shown to decrease mortality and morbidity in patients with HFrEF by reducing sodium absorption in the renal tubules, thereby improving LV remodeling mainly by inhibiting the metabolism of myocardial muscle fibers, subsequently reducing cardiac myocyte necrosis and fibrosis and decreasing the risk of reentrant ventricular arrhythmias and sudden death of a cardiac etiology [12].

Results

1. Today the survival in patients with advanced stages of cancer has improved with new therapeutics such as the monoclonal antibodies targeting HER-2 including trastuzumab and pertuzumab, as well as many others.
2. Due to combination chemotherapies that are being increasingly utilized to treat patients with advanced stages of cancer, it is very critical to identify early, at-risk patients for cardiac complications.
3. TTE with strain imaging may help guide prevention and management of CTRCD with early detection of subclinical cardiomyopathies in patients receiving HER2-based chemotherapies.
4. This case report emphasizes the importance of increased awareness, vigilant monitoring, and multidisciplinary team involvement for high-risk cardiac patients receiving HER-2 (trastuzumab and pertuzumab) combination-based CT.
5. CO protocol risk assessment algorithm for patients who will be started on HER-2 based targeted therapy can guide oncologists for referring patients prior to chemotherapy to best provide CO support to high-risk patients.

Authors' Contributions

Dr. Lalitha C Medepalli: Lead author, corresponding author, Cardio-Oncologist on the case involved in the patient care, preparing, coordinating and editing the manuscript

Dr. Kristy McDonald-Grimm: Oncologist on the case, involved in the patient care

Dr. Brenda Hott: Advanced heart failure specialist on the case, involved in the patient care

Dr. Cheryl F Jones: Oncologist- editing and expert opinion

Dr. Vidya M Medepalli: Resident physician editing and preparing the manuscript

Dr. Srinivas Saripalli: Resident physician editing and preparing the manuscript

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