Use of Entresto (sucubitril/valsartan) in Anthracycline Induced Cardiomyopathy

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Background: Entresto significantly reduce cardiovascular mortality and hospitalizations due to systolic heart failure (HF) with reduced ejection fraction (HFrEF), when compared to standard HF therapy. Though Entresto has not been evaluated in patients with HFrEF secondary to chemotherapy, current Canadian Cardiovascular Society (CCS) cardio-oncology guidelines recommend that patients who develop clinical HF or an asymptomatic decline in LVEF during or after treatment should be managed according to the CCS Heart Failure Guidelines, including the use of Entresto. We present data from two patients who experienced chemotherapy induced HFrEF managed with Entresto after failing to respond to standard therapy.

Case Comparison: Patient A (female, age 65) received doxyrubicin for mantle cell lymphoma, Patient B (female, age 76) received epirubicin and left chest wall radiation for HER-2 negative breast cancer. Both patients were initiated on cardio-protective medications for symptomatic HFrEF, including angiotensin-converting enzyme inhibitors, beta blockers, mineralocorticoid receptor antagonists and diuretics. Patient A presented a year post anthracycline exposure, Patient B 14 years post. Both patients remained dyspneic despite optimal medical therapy and were switched from an ACEI to Entresto. Patient A experienced a decline in NTproBNP (68281 ng/L to 14130 ng/L) 2 weeks following initiation and reported an improvement in dyspnea. She was titrated to a target dose of 200 mg twice daily without complications. Patient B developed hypotension but tolerated 50 mg twice daily. Both patients remained on additional heart failure therapies. At the time of writing, neither patient has required re-intervention by the Cardio-Oncology Clinic or admission to hospital.

Discussion: We report 2 cases of patients with reductions in LVEF secondary to chemotherapy, managed with Entresto, who experienced an improvement in NTproBNP and HF symptoms, without experiencing HF related hospitalizations and adverse drug effects. Though we do not know long-term efficacy and safety of Entresto in anthracycline-induced cardiotoxicity, our experience demonstrates Entresto may be a potential option in this highly complex patient population.

References:

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Abstract Character Count (excluding spaces, authors, affiliations and references): 2000

A 68 year old female with a history of mantle cell lymphoma treated with anthracycline-based induction chemotherapy followed by melphalan, total body irradiation and autologous stem cell transplantation. Field radiotherapy to the left hemipelvis was also completed and the patient received maintenance rituximab every 3 months for a planned 8 cycles. Baseline MUGA findings demonstrated a normal LVEF of 0.73,echocardiogram suggested LVEF 54% by Simpson's biplane measurement.

One year following initial administration of chemotherapy, the patient was referred to the cardiology-oncology clinic at South Health Campus in Calgary, Alberta and was found to be in NYHA functional class II; repeat ECHO revealed moderately reduced left ventricular systolic function with an LVEF of 33%, mildly reduced right ventricular systolic function, elevated pulmonary artery pressure and a small circumferential pericardial effusion. A right heart catheterization confirmed elevated left sided filling pressures and NT-proBNP was elevated at29175 ng/L.

The patient was diagnosed with non-ischemic cardiomyopathy secondary to anthracycline toxicity and was initiated on evidence based heart failure medications: bisoprolol, perindopril (switched to candesartan secondary to cough), spironolactone, furosemide and a nitroglycerin patch and titrated to target or maximum tolerated doses. Despite 6 weeks of therapy with cardioprotective medications, the patient's NT-proBNP continued to rise up to 68281 ng/L. At this time candesartan was switched to Entresto, as the increase in NT-proBNP was thought to be related to elevated left sided filling pressure in the setting of high mean systemic arterial pressure. Within 1-2 weeks of initiating Entresto the patient stated that her shortness of breath symptoms had nearly resolved and that she was nearly back to her baseline level of function. Consequently, her repeat NT-proBNP dropped to 14130 ng/L. Medications were tolerated well and the plan was to reimage the heart using a cardiac MRI six months after further up-titration. No hospitalizations for heart failure have occurred. The patient is currently stabilized on Entresto 200 mg twice daily.

Case 2: A 75 year old female with a history of ER/PR positive HER-2 negative left sided breast cancer initially presenting in 2002, managed with a radical mastectomy followed by FEC (5-fluoruracil, epirubicin, cyclophosphamide) chemotherapy, radiation, and tamoxifen for 5 years followed by letrozole (discontinued due to intolerance). Two years ago, she presented with a metastatic recurrence with to bone, liver and a malignant pleural effusion currently treated with anastrazole and clodronate.

Last fall, the patient was admitted to the emergency department with swollen feet. Echocardiogram confirmed congestive heart failure with a dilated left ventricle with an LVEF of 25%, moderate to severe mitral regurgitation. The patient was diagnosed with a cardiomyopathy likely due to previous anthracycline therapy and left-sided chest radiation and initiated on carvedilol, enalapril, eplerenone, and furosemide. During her 3 month follow up visit, the patient's pedal edema had improved and she was tolerating therapy well with the exception of occassional hypotension secondary to hypovolemia. Repeat echocardiogram revealed worsening results with a an EF of 25%, a mild to moderately dilated right ventricle with moderately reduced right ventricular systolic function, biatrial enlargement, moderate tricuspid regurgitation, and elevated pulmonary artery pressure. A NT-proBNP drawn earlier in the month was 3050 ng/L and rose to 4676 ng/L two weeks later. Following this, the patient was switched from enalapril to Entresto 50 mg bid and furosemide was discontinued. Further uptitration has not been possible as the patient's SBP remains in range of the 90-100 mm Hg, however symptoms of lightheadness and dizziness have been minimized by staggering blood pressure lowering medications. The patient is otherwise tolerating therapy well and has not been readmitted to hospital due to heart failure.

NT-proBNP as a surrogate marker for worsening heart failure, goal of therapy is to prevent further decline in cardiac function, prevent hospitalizations, maintain quality of life, remain heart failure symptom free and improve mortality.