The Use of Entresto (sacubitril/valsartan) in Anthracycline-Induced Cardiomyopathy

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BACKGROUND

PARADIGM-HF:
- Sacubitril/valsartan significantly reduced the composite of cardiovascular mortality or heart failure hospitalizations in adult patients in NYHA II-IV, with a reduced ejection fraction (HFrEF) and elevated NT-proBNP when compared to enalapril (HR 0.80; p < 0.001, 95% CI 0.73-0.87)
- When examined individually, the absolute risk reduction of death from cardiovascular causes was 3.2% (NNT=31) and heart failure (HF) hospitalization was 2.8% (NNT=36)
- More symptomatic hypotension in sacubitril/valsartan group but less elevations in serum creatinine and potassium
- Median NT-proBNP ~1600 pg/ml; changes not reported
- Sacubitril/valsartan has not been evaluated specifically in patients with HFrEF secondary to chemotherapy

Canadian Cardiovascular Society1,2:
- Combination of ACE inhibitors (or ARB), mineralocorticoid receptor antagonists and beta blockers, with diuretics for volume management
- Sacubitril/valsartan recommended in place of ACE inhibitor (or ARB) for patients with mild to moderate HF with elevated NT-proBNP or hospitalization in prior 12 months
- Management of cancer patients who develop clinical HF or an asymptomatic decline in LVEF (e.g. >10% decrease in LVEF from baseline or LVEF <53%) during or after treatment recommended to follow current Heart Failure Guidelines

OBJECTIVES & METHODS

To present longitudinal, observational data from two patients followed in the Cardio-Oncology clinic who experienced chemotherapy-induced reductions in LVEF and are currently managed with sacubitril/valsartan in addition to evidence based HF therapies

RESULTS

CASE A
- Patient: 68F diagnosed in 2015 with mantle cell lymphoma, stage II versus IV (uncertain if lung nodules are lymphoma), currently in complete remission
- Cancer Therapy:
  - Induction chemotherapy R-CHOP/R-DHAP (cisplatin discontinued after 1st cycle due to renal insufficiency) x 6 cycles
  - Cumulative doxorubicin dose: 161 mg/m²
  - Melphalan, total body irradiation and autologous stem cell transplantation
  - Involved field radiotherapy
  - On current treatment with maintenance rituximab
- Imaging:
  - Baseline: MUGA: normal LVEF 0.73
  - 3 month: ECHO: low-normal LVEF 54%, abnormal peak strain (-18%)
  - 12 months post-chemo: ECHO: moderately reduced LVEF of 33%, mildly reduced RV systolic function, RVSF 64.8 mmHg, small pericardial effusion
  - Right heart catheterization: elevated left sided filling pressures, elevated systemic vascular resistance, CVP 12 mmHg, PCWP 21 mmHg, CO 3.9 L/min, CI 2.4 L/min/m²
  - 3 months post sacubitril/valsartan initiation: CMR: normal LVEF 59%, subepicardial late enhancement suggests non-ischemic myocardial fibrosis
- Biomarkers:
  - HF diagnosis: NT-proBNP 29175 ng/L
  - 6 weeks after HF therapy initiated: NT-proBNP 68281 ng/L
  - 2 weeks post sacubitril/valsartan initiation: NT-proBNP 14130 ng/L
  - 3 months post sacubitril/valsartan: NT-proBNP 2783 ng/L
- HF Therapy:
  - Bisoprolol, perindopril (switched to candesartan due to cough)
  - Spironolactone, nitrolycerin patch, furosemide prn
- HF Course:
  - NYHA II, presented with fatigue, orthopnea, dyspnea, HTN
  - Dyspnea worsened despite medical therapy, managed with additional clinic visits
  - HF symptoms improved with initiation of sacubitril/valsartan
  - No hospitalizations for HF
  - Stabilized on sacubitril/valsartan 200 mg bid and bisoprolol 10mg daily
- Imaging:
  - Baseline: MUGA: normal LVEF 0.73
  - 3 month: ECHO: low-normal LVEF 54%, abnormal peak strain (-18%)
  - 12 months post-chemo: ECHO: moderately reduced LVEF of 33%, mildly reduced RV systolic function, RVSF 64.8 mmHg, small pericardial effusion
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  - HF symptoms improved with initiation of sacubitril/valsartan
  - No hospitalizations for HF
  - Stabilized on sacubitril/valsartan 200 mg bid and bisoprolol 10mg daily

CASE B
- Patient: 75F initially diagnosed in 2001 with breast cancer, metastatic recurrence in 2014
- Cancer Therapy:
  - Radical mastectomy, FEC chemotherapy and left chest radiation
  - Melphalan, total body irradiation and autologous stem cell transplantation
  - Involved field radiotherapy
  - On current treatment with anastrazole and zoledronic acid
- Imaging:
  - Baseline: MUGA: normal LVEF 0.73
  - 3 month: ECHO: low-normal LVEF 54%, abnormal peak strain (-18%)
  - 12 months post-chemo: (at HF presentation)
  - ECHO: moderately reduced LVEF of 33%, mildly reduced RV systolic function, RVSF 64.8 mmHg, small pericardial effusion
  - Right heart catheterization: elevated left sided filling pressures, elevated systemic vascular resistance, CVP 12 mmHg, PCWP 21 mmHg, CO 3.9 L/min, CI 2.4 L/min/m²
  - 3 months post sacubitril/valsartan initiation: CMR: normal LVEF 59%, subepicardial late enhancement suggests non-ischemic myocardial fibrosis
- Biomarkers:
  - HF diagnosis: NT-proBNP 29175 ng/L
  - 6 weeks after HF therapy initiated: NT-proBNP 68281 ng/L
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- HF Therapy:
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  - Spironolactone, nitrolycerin patch, furosemide prn
- HF Course:
  - NYHA II, presented with fatigue, orthopnea, dyspnea, HTN
  - Dyspnea worsened despite medical therapy, managed with additional clinic visits
  - HF symptoms improved with initiation of sacubitril/valsartan
  - No hospitalizations for HF
  - Stabilized on sacubitril/valsartan 50 mg bid, carvedilol 12.5mg qid and eplerenone 25 mg daily

DISCUSSION

- We report our findings from two patients with reductions in left ventricular ejection fraction (LVEF) secondary to chemotherapy who were managed with sacubitril/valsartan with notable improvements in HF symptoms
- To date, neither patient has experienced HF hospitalizations nor significant adverse drug effects
- Although NT-proBNP is a surrogate marker for worsening HF, we demonstrate favourable findings for the improvement in HF symptoms and quality of life, prevention of further decline in cardiac function, and prevention of HF hospitalizations
- Both patients had improved RV function, Case A also experienced marked improvement in LV systolic function

CONCLUSION

- Based on these findings and the current Canadian Cardiovascular Society Heart Failure Guidelines for patients with HFrEF, sacubitril/valsartan may be considered as a second line option in this patient population
- Further studies are required to assess long-term efficacy & safety and impact on morbidity & mortality

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- The information presented has been shared with the explicit consent of the patients
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