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Cardiotoxicity: Role of Sacubitril-Valsartan in Heart Failure with Reduced Ejection Fraction and Cancer with Hepatic Metastasis

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ABSTRACT

The aim of this report is to describe the impact of pharmacological treatment with sacubitril/valsartan in a patient with stage IV colon cancer.

We describe the case of a 69-year-old woman with heart failure with reduced ejection fraction and the diagnosis of colon cancer with hepatic metastasis. By the time of the diagnosis, the patient was already under titration of sacubitril/valsartan with tolerability up to the maximum dose.

Due to the optimized heart failure treatment, the patient underwent surgery and initiated chemotherapy without any cardiovascular complications, demonstrating that sacubitril/valsartan was safe in this complex situation.

Keywords

ARNI, Colon cancer, Heart failure, Metastatic disease, Sacubitril/valsartan.

Introduction

Sacubitril/valsartan is indicated for the treatment of symptomatic heart failure with reduced ejection fraction (HF-REF) [1].

Up to the present time, there are no Randomized Controlled Trials with sacubitril/valsartan in patients with active cancer. In the PARADIGM-HF study, the only patients included were those with a previous diagnosis of cancer, mostly diagnosed more than five years before [2]. Maurea N and colleagues evaluated whether sacubitril/valsartan administered during treatment with doxorubicin, trastuzumab or pertuzumab, was able to reduce the cardiotoxicity induced by these anti-neoplastic drugs, compared to valsartan alone, having concluded that sacubitril/valsartan increases the viability of cells treated with anti-neoplastic agents, thus reducing their cardiotoxic effects *in vitro* [3,4].

In this context, we intend to describe the safety of pharmacological treatment with this drug in a patient with hepatic metastasis, who underwent surgery and a potentially cardiotoxic chemoterapy regimen without any cardiovascular decompensation.

Case Report

A 69-year-old woman with a previous history of metabolic syndrome, atrial fibrillation (hypocoagulated), ferropenic anaemia and hypothyroidism has been diagnosed with HF-REF due to ischemic etiology.

One year before, she experienced a non-ST elevation myocardial infarction (NSTEMI) treated by percutaneous coronary intervention of the right coronary artery and proximal circunflex. The echocardiogram post-NSTEMI showed a reduced ejection fraction (Left Ventricular Ejection Fraction = LVEF of 30-35%) and it was decided to refer the patient to the Hospital's Heart Failure Clinic (HFC) (Table 1).

At the first HFC appointment, she was on functional class III of the New York Heart Association (NYHA), with a blood pressure of 160/80 mm Hg, a N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 13092 pg/mL, a moderately depressed renal function (estimated Glomerular Filtration Rate – eGFR –

calculated by the CKD-EPI formula of 42 mL/min/1.73m^2) and a normal liver function (Child-Pugh Classification of Cirrhosis A).

Table 1: Echocardiographic and analytical progression before and during treatment with Sacubitril/Valsartan.

	Before starting	Two months after starting	Ten months after starting
NYHA* Functional Class	III	III	II
NT-proBNP § - pg/mL	13092	9850	3985
Blood Pressure - mm Hg	160/80	123/54	115/52
Echocardiogram (LVEF) ¶	30-35%	30-35%	30-35%
eGFR † (mL/min/1.73m^2)	42	37	26
Serum potassium (mmol/L)	4.9	4.4	4.1
Child-Pugh ‡	5	5	5
Lee's Criteria &	High Risk (> 11%)		
MAGGIC Score #	16	12	12

* New York Heart Association (NYHA) class reflects the status of patients
§ NT-proBNP denotes N-terminal pro-B-type natriuretic peptide plasma levels expressed as pg/mL (equivalent to ng/L, SI units)
¶ LVEF stands for Left Ventricular Ejection Fraction (%)
† Estimated Glomerular Filtration Rate (eGFR) expressed as mL/min/1.73m^2 calculated by the CKD-EPI formula
‡ Child-Pugh Classification of Cirrhosis: Class A: 5-6 points (1-year survival 100%); Class B: 7-9 points (1-year survival 80%); Class C: 10-15 points (1-year survival 45%)
& Revised Cardiac Risk Index (Lee's Criteria): Risk for cardiac death, nonfatal myocardial infarction and nonfatal cardiac arrest: 0 predictors = 0.4%; 1 predictor = 0.9%; 2 predictors = 6.6%; > 3 predictors = 11%
# MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) Score: Mortality Risk Score at 1 and at 3 years: 16 points (7.0% 1-year mortality and 17.5% 3-year mortality); 12 points (4.8% 1-year mortality and 12.2% 3-year mortality).

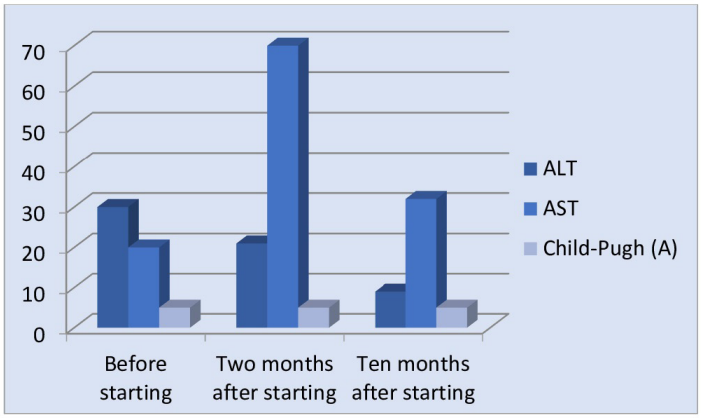

Figure 1: Analytical progression before and during treatment with Sacubitril/Valsartan. ALT stands for Alanine Aminotransferase and AST for Aspartate Aminotransferase in IU/L.

Previoulsy, she had been medicated with ramipril 10 mg, bisoprolol 5 mg, acetylsalicylic acid 100 mg, edoxaban 60 mg, atorvastatin 80 mg, levothyroxin 0.05 mg, spironolactone 12.5 mg and pantoprazole 20 mg.

At that time, the patient reported that she had stopped anticoagulation due to bloody stools and we decided to investigate the cause of lower gastrointestinal (GI) bleeding (in the past, she had refused endoscopic evaluation for the ferropenic anaemia).

In order to optimize the HF treatment, we decided to suspend spironolactone due to hyperkalaemia and switch from ramipril to sacubitril/valsartan in the 24/26 mg bid dose, after a washout period. In the next six weeks, we were able to uptitrate sacubitril/valsartan with good tolerance (Table 1). In the meantime, the patient was diagnosed with sigmoid colon adenocarcinoma, with hepatic metastasis. By the time of that diagnosis, the patient was already tolerating the 49/51 dose of sacubitril/valsartan with non-invasive blood pressure of 123/57 mm Hg, eGFR of 37.2 mL/min/1.73m^2 and NT-proBNP level of 3985 pg/mL. She improved her NYHA functional class from III to II and remained in Child-Pugh Class A (Table 1). At this point, we decided to increase sacubitril/valsartan to the maximum dose (97/103 mg bid) in order to further optimize HF treatment. Regarding cancer treatment, the patient underwent sigmoidectomy without complications and due to liver metastasis was started on adjuvant chemotherapy with FOLFIRI (FOLinic Acid, Fluorouracil, IRInotecan) [5]. Despite the cardiotoxic potential of this regimen (mainly coronary vasospasm or even myocardial dysfunction induced by fluorouracil), the patient remained stable without any hospitalization or emergency department visit due to a cardiovascular cause.

One month after starting chemotherapy, the FOLFIRI regimen had to be suspended due to intestinal mucositis and the patient ultimately died of septic shock in the context of induced neutropenia.

Discussion

Sacubitril/valsartan is indicated for the treatment of HF-REF to reduce the rate of cardiovascular death and hospitalizations due to decompensated heart failure [1].

According to Gregorietti V and collaborators, in patients with ventricular dysfunction secondary to chemotherapy and refractory to conventional therapy, sacubitril/valsartan improved left ventricular ejection fraction and led to normalization of NT-proBNP levels in all patients [6]. In the study by Ana Martín-Garcia et al., the results suggested that sacubitril/valsartan is well tolerated and improves left ventricular function, NT-proBNP levels and symptomatic status in cancer therapy-related cardiac dysfunction, but they referred exclusively to haematological neoplasms [7].

Our case report illustrates a patient with HF-REF and stage IV cancer with hepatic metastasis that had been optimized with sacubitril/valsartan.

Considering that hepatic dysfunction is prevalent in patients with heart failure and in this scenario the patient had metastatic liver disease, one could fear a challenging titration of sacubitril/

valsartan. There is limited clinical experience with sacubitril/valsartan in patients with moderate hepatic impairment (Child-Pugh B) or with Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) values more than twice the upper limit of the normal range and this drug is contraindicated in patients with severe hepatic impairment (Child-Pugh C) [1]. However, the patient was on Child-Pugh class A and, during the follow-up, liver function remained stable (Figure 1). According to the Suzuki K et al. study, sacubitril/valsartan may have beneficial effects on patients' liver function parameters that are prognostically important in HF-REF [8].

Moreover, impaired kidney function is one of the strongest predictors of outcomes in heart failure [9]. In the PARADIGM-HF study, sacubitril/valsartan delayed renal progression in patients with HF-REF [2]. In the article by Alex H et al., sacubitril/valsartan was safe and led to a symptomatic improvement in patients with severe heart failure undergoing hemodialysis [10].

Although our patient had progression of renal dysfunction, mainly near the final hospital admission due to septic shock, is important to underline that she had never developed hyperkalaemia or needed dialysis under treatment with sacubitril/valsartan.

Despite being a high risk patient, according to the Modified Lee Criteria (more than 11% risk for cardiac death, nonfatal myocardial infarction and nonfatal cardiac arrest) and to the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) Score with a predicted mortality risk at 1 year/3 year of 7%/12%, respectively, the patient remained stable, without any cardiovascular complication throughout the spectrum of interventions regarding cancer treatment, including a potentially cardiotoxic chemotherapy regimen [11].

Taking into account the patient's ejection fraction, one might have thought about implanting an Implantable Cardioverter Defibrillator, however, it is not indicated in patients with a life expectancy less than twelve months.

Conclusion

Sacubitril/valsartan is indicated for the treatment of symptomatic heart failure with reduced ejection fraction (HF-REF) [1].

Up to the present time, there are no Randomized Controlled Trials with sacubitril/valsartan in patients with active cancer.

We describe the safety of pharmacological treatment with this drug in a patient with colorectal cancer and hepatic metastasis, who underwent surgery and a potentially cardiotoxic chemoterapy regimen without any cardiovascular decompensation.

Giving the good tolerance, with improvement of the patient's functional status, NT-proBNP and liver function, despite an absence of objective improvement in echocardiographic parameters, sacubitril/valsartan demonstrated to be safe in this highly complex situation and we encourage its use in similar cases.

Conflicts of interest

The second and the last authors have received speaker honoraria from the Novartis Company and grants from the Servier Company.

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