


Sacubitril/Valsartan to Treat Heart Failure in a Patient with Relapsing Hairy Cell Leukaemia: Case Report

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ABSTRACT: Experience with angiotensin-receptor neprilysin inhibitors (ARNI) in oncologic patients with heart failure (HF) is limited. We report a case of ARNI started as first-choice therapy in a patient with relapsing hairy cell leukaemia (HCL) and HF with depressed left ventricular ejection fraction (LVEF). A middle-aged male, previously treated with rituximab for HCL, was scheduled for cardiologic screening before starting a new antineoplastic therapy for cancer relapse. The patient had symptomatic HF with reduced LVEF and high NT-proBNP levels. In this patient, early ARNI treatment was well tolerated and produced a rapid and durable improvement of symptoms, LVEF and NT-proBNP levels. Consequently, the oncologic team could start an experimental treatment with obinutuzumab, with complete HCL remission. In conclusion, in this patient with HCL and HF, ARNI therapy was safe and effective, contributing to undelayed cancer treatment.

KEYWORDS: Sacubitril/valsartan, ARNI, heart failure, chemotherapy, hairy cell leukaemia

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Introduction

In the PARADIGM-HF study, the angiotensin-receptor neprilysin inhibitor (ARNI) sacubitril/valsartan was superior to angiotensin-converting enzyme (ACE) inhibition in decreasing both mortality and hospitalisation rates in symptomatic patients with heart failure and depressed left ventricular ejection fraction (HFrEF).¹ However, in PARADIGM-HF, only stable patients in therapy with ACE inhibitors were eligible to join the study and patients with active oncologic disorders were substantially excluded from the study due to their short life expectancy.

Oncologic patients often suffer from (HFrEF), mainly due to the cardiotoxicity of antineoplastic treatments,² and many of them carry a significant lifetime risk of death or hospitalisation for heart failure.³ Moreover, a depressed left ventricular ejection fraction (LVEF) often precludes patients with cancer from receiving full doses and complete courses of antineoplastic treatments.⁴ Thus, oncologic patients with HFrEF might benefit from the addition of ARNI to their heart failure treatment, and early ARNI administration might be of great value to prevent irreversible myocardial damage and to allow more patients to complete their antineoplastic drug schedule.

Unfortunately, data on tolerability and outcomes of oncologic patients with HFrEF treated with ARNI are lacking.

Case report

A 45-year-old Caucasian male underwent cardiologic screening before starting a new antineoplastic treatment for relapsing hairy cell leukaemia (HCL). The patient was diagnosed with HCL in 2014 and had been treated with cladribine (continuous infusion of 0.09 mg/kg for 7 days) followed by rituximab (8 cycles of 375 ml/m²) with complete clinical remission. At that time, baseline and follow up echocardiography were unremarkable.

At the screening outpatient visit before starting chemotherapy for the HCL relapse, the patient reported a history of allergic asthma in childhood/adolescence treated with inhaled corticosteroids and bronchodilators and slight hypercholesterolemia. During the visit, the patient complained of mild exertional dyspnea started 2 to 3 months earlier. Physical examination showed a blood pressure of 120/80 mmHg, a heart rate of 85 bpm, a soft mitral grade 2/6 regurgitation murmur, bilateral basal crackling rales and mild and symmetrical calf swelling. The twelve-leads ECG demonstrated sinus rhythm and non-specific repolarisation abnormalities. Nt-proBNP was significantly above the normal range while high sensitivity troponin I was only slightly elevated (Table 1). Echocardiography demonstrated mildly enlarged left heart chambers with severely impaired LVEF, impaired diastolic function, trivial mitral and tricuspid regurgitation with increased tricuspid regurgitation



Table 1. Symptoms, vital signs, laboratory parameters and therapy.

	BASELINE	FOLLOW UP		
		1 MO	6 MO	12 MO
NYHA class	2	1	1	1
Heart rate (bpm)	85	75	70	67
Blood pressure (mmHg)	120/80	110/70	105/70	110/65
Haemoglobin (g/dL)	11.1	12.4	12.6	13.8
Haematocrit (%)	36	40	42	48
NT-proBNP (pg/mL)	2400	780	600	440
Hs cTnI (pg/mL)	0.20	0.19	0.16	0.14
K ⁺ (mEq/L)	4.4	3.9	3.7	3.9
Creatinine (mg/dL)	0.76	0.88	0.87	0.90
eGFR (ml/min/1.70m ² BSA)	89	78	76	80
Therapeutic schedule				
Furosemide	25 mg (bid the 1st week, then od)	25 mg	none	none
Canrenone	50 mg od	50 mg od	50 mg od	50 mg od
Sacubitril/valsartan	24/26 mg bid	49/51 mg bid	49/51 mg bid	49/51 mg bid

Abbreviations: BSA, body surface area; eGFR, calculated glomerular filtration rate; Hs cTnI, high-sensitivity cardiac troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York heart association.

Vital signs and laboratory parameters at baseline and 1, 6 and 12 months after starting sacubitril/valsartan.

gradient (Table 2). Cardiac Magnetic Resonance (CMR) excluded focal myocardial inflammation and focal fibrosis; parametric sequences showed slightly elevated values of native T1 and ECV, globally suggestive for the presence of mild and diffused interstitial fibrosis (Figure 1). CT coronary angiography showed the absence of coronary artery atherosclerosis (Figure 2).

Sacubitril/valsartan 24/26 mg bid was started immediately and, after 2 weeks, was up titrated to 49/51 mg bid. Beta-blockers were not prescribed due to the history of asthma. At 1 month follow up NT-proBNP serum levels decreased significantly (Table 1), and echocardiography documented a recovery to nearly-normal values of LVEF with improved left ventricular diastolic function and reduced tricuspid gradient (Table 2). This clinical trend continued at 6 and 12 months follow up with LVEF persistently in the normal range and without undesired pharmacologic side effects (Table 1 and 2).

One month after the beginning of sacubitril/valsartan therapy, the patient could start an experimental treatment with 6 cycles of Obinotuzumab 900 mg daily with a complete and persistent clinical remission at 1 year follow up.

Discussion

There is an unmet need for data on treatment with ARNI in oncologic patients with heart decompensation and cardiotoxicity. Though sacubitril/valsartan showed better clinical outcomes than enalapril in symptomatic patients with HFrEF in

PARADIGM-HF,¹ the results apply to patients who presented with stable clinical characteristics. In particular, patients with oncologic disorders (included cardiotoxicity due to antineoplastic treatments) were almost entirely excluded from the trial due to their short life expectancy.

Patients with cancer often suffer from HFrEF, mainly, but not exclusively, due to the cardiotoxicity of antineoplastic treatments² and many of them carry a significant lifetime risk of death or hospitalisation for heart failure.³ Moreover, a depressed LVEF often limits or precludes these patients from receiving full doses and complete courses of pharmacologic antineoplastic treatments which are indispensable as second- and third-line therapeutic agents.⁴ Drugs currently employed for HFrEF treatment are sufficient to treat chemotherapy-related cardiotoxicity, but often cardiac damage is not fully reversible.⁴ In the present case, CMR showed mild abnormalities like elevated values of native T1 and ECV. These findings might therefore represent subclinical cardiac damage, likely outcomes of prior cardiotoxic cancer treatments.⁵

Subclinical myocardial damage can result from exposition to cardiotoxic cancer therapies, even in the absence of overt LVEF depression and clinical HFrEF.⁶ Some studies have tested ACE-inhibitors and beta-blockers for preventing and treating cancer therapy cardiotoxicity, unfortunately with inconclusive results.⁷ Thus, early addition of ARNI to standard treatment in oncologic patients with HFrEF might be valuable either for preventing irreversible myocardial damage or for

Table 2. Echocardiographic parameters.

	BASELINE*	EVALUATION FOLLOWING HCL RELAPSE	FOLLOW UP		
			1 MO	6 MO	12 MO
LA volume/BSA (mL/m ²)	29	33	30	29	30
LV diastolic diameter/BSA (cm/m ²)	3.0	3.6	3.3	3.1	3.2
LV diastolic volume/BSA (mL/m ²)	67	87	80	76	67
LV systolic volume/BSA (mL/m ²)	22	57	36	30	24
LVEF %	65	35	55	61	64
A wave (cm/s)	30	48	45	38	33
E wave (cm/s)	40	34	32	47	46
E/A ratio	1.33	0.71	0.71	1.24	1.39
Deceleration time (ms)	180	234	203	190	185
E/E'	4.6	12.6	10.1	7.9	4.9
Mitral regurgitation degree	±	2	1	1	1
Estimated right atrial pressure (mmHg)	<5	15	15	<5	5-10
Tricuspid regurgitation gradient (mmHg)	21	44	29	22	23

Abbreviations: BSA, body surface area; LA, left atrium; LVEF, left ventricular ejection fraction. Echocardiographic parameters at baseline and 1, 6 and 12 months after starting sacubitril/valsartan. *Follow up echocardiography performed 1 y before the current clinical presentation.

allowing more patients to complete their antineoplastic drug schedule.

Sacubitril-valsartan administration before or immediately after discharge in patients with HFrEF has been proved feasible and safe in the TRANSITION study.⁸ Furthermore, in the PIONEER-HF study, an even earlier start of ARNI during hospitalisation for acute heart failure has been shown to provide clinical benefits in terms of more rapid reduction of NT-proBNP levels and prevention of early re-hospitalisation for heart failure.⁹

Unfortunately, published data about the efficacy and safety of ARNI in patients with cancer and HFrEF are minimal and, to our knowledge, there are no reports of patients with HFrEF treated with sacubitril/valsartan following a relapsing haematological malignancy. The caution with which new therapies, such as ARNI, are introduced in cancer patients is understandable. Oncologic patients often suffer from comorbidities due to advanced age, coexisting diseases and the adverse effects of the neoplastic disease itself and the antineoplastic drugs over renal function and hydro-electrolytic balance. Thus the prevalences of hypotension, impaired renal function and hyperkalemia are increased in this population,¹⁰ making ARNI start and titration more complicated than in standard HF patients. Sheppard et al¹¹ presented for the first time data from 2 patients with anthracycline-induced cardiomyopathy successfully managed with ARNI after suboptimal responses to traditional evidence-based heart failure therapies. In another recent case series, Martin-Garcia et al¹² reported the effects of sacubitril/

valsartan on left ventricular ejection fraction (LVEF) and reverse remodelling parameters in 10 consecutive patients with cancer therapy-induced cardiomyopathy and HFrEF evaluated with cardiac magnetic resonance before and 3 months following the initiation of ARNI therapy. In this population, the median time from cancer therapy to HFrEF was 31 months and the drugs employed were mostly anthracyclines. In this small sample, the authors observed a significant reduction in left ventricular volumes and a significant improvement in LVEF, NT-proBNP levels and symptoms regardless of the dose of ARNI received.

Thus the vast majority of the patients with cancer therapy cardiotoxicity treated with ARNI reported so far had been previously exposed to anthracyclines, and only a few received exclusively novel 'targeted' antineoplastic treatments. Current treatment protocols for HCL include drugs with limited potential for cardiotoxicity² and, in particular, no reports of significant cardiovascular adverse effects were retrieved in a thorough literature search for cladribine, 1 of the 2 antineoplastic drugs assumed by our patient at the time of the first HCL occurrence. The other, rituximab, have been linked to non-ischemic HFrEF in various reports.¹³ The occurrence of HF has also been observed late after the exposition to the drug.¹⁴ Nevertheless, a delayed occurrence of cancer therapy-related cardiotoxicity following exposition to rituximab seems unusual.¹⁴ Thus the origins of myocardial dysfunction in our patient remain elusive, and the link with previous antineoplastic treatments is speculative.

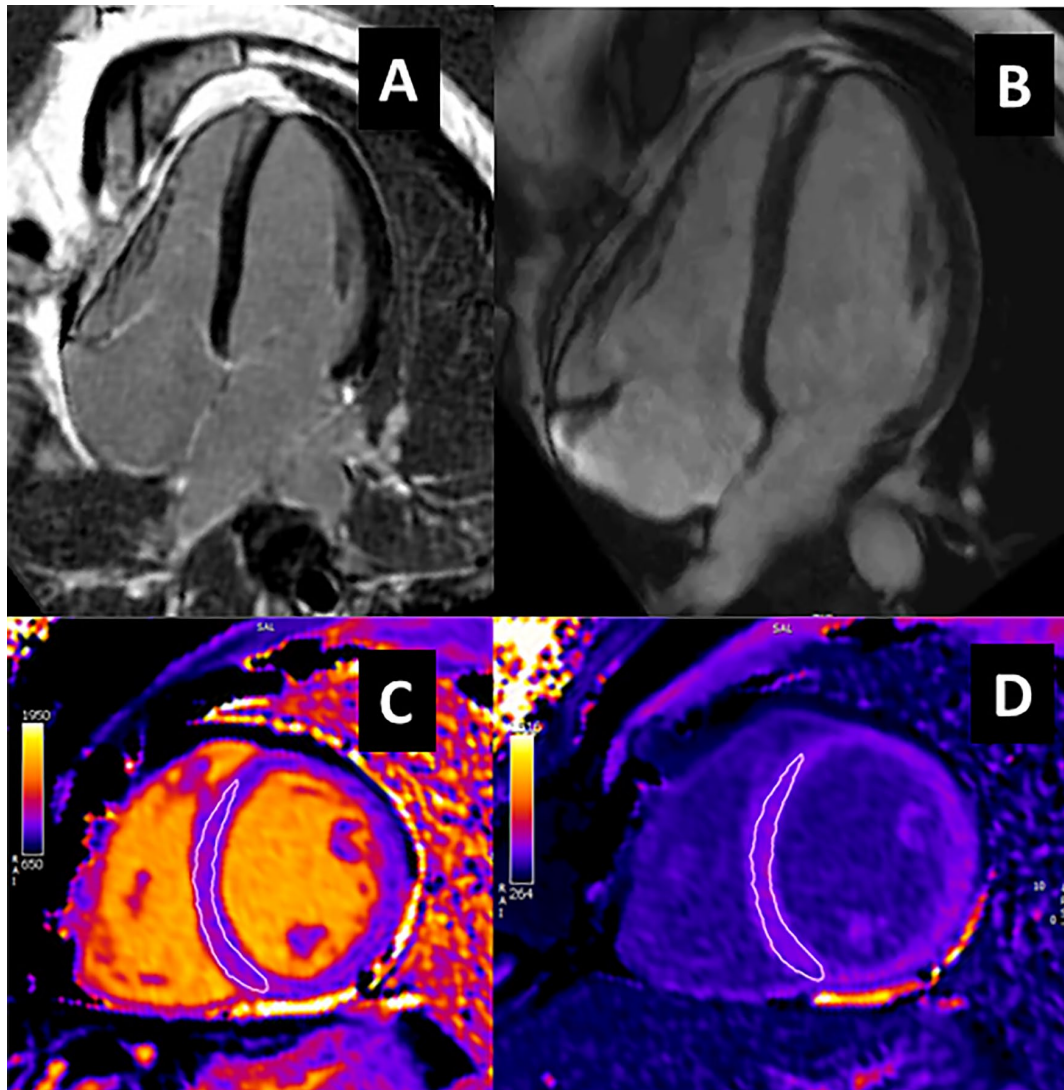


Figure 1. Cardiac magnetic resonance showing the absence of signs of acute inflammation and scarring: (A) the 4-chamber view shows the lack of areas of late gadolinium enhancement, (B) is represented an SSFP image in 4-chamber view. (C) is reported a short axis native T1 mapping, with the ROI in the septum showing a value of 1019 ± 27 msec (normal < 1010 msec), and (D) post-contrast T1 allowed an estimate of the extracellular volume of $28 \pm 2\%$.

In the present case report, ARNI administration was followed within a few weeks by a significant reduction of natriuretic peptides and an impressive regression of left ventricular remodelling. The rapid improvement of left ventricular systolic function was a crucial clinical result because it prevented dangerous delays in starting antineoplastic treatment. However, ARNI treatment was initiated in the presence of fluid overload, clinically demonstrated by bilateral basal crackling rales, mild calf swelling and, at echocardiography diastolic dysfunction and increased tricuspid regurgitation gradient. The concomitant administration of diuretics probably contributed to the recovery of left ventricular ejection fraction and the reduction of Nt-proBNP levels. However, the beneficial effect of early ARNI administration probably played the most crucial role. Even if the magnitude of ARNI-related reverse remodelling described in previous studies is inferior to that observed in our case,¹⁵⁻¹⁷ other studies showed more considerable changes of left ventricular volumes and ejection fraction.^{12,18,19} Moreover,

in the present case the observed changes of left ventricular volumes and ejection fraction improvement were rapid, similarly to other reports describing significant reverse remodelling only after switching from standard therapy to sacubitril/valsartan in patients with cardiotoxicity.²⁰

In conclusion, in this case report of relapsing HCL and HFrEF, early ARNI treatment was feasible, safe and accompanied by significant LVEF improvement. This prompt management of HFrEF probably contributed to a timely, efficient and uneventful antineoplastic therapy.

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Authors' contributions

Alessandro Lupi drafted and gave the final approval to the manuscript, Sara Ariotti, Doranna De Pace, Stefano Bertuol and Irene Ferrari contributed to manuscript drafting, Lorenzo

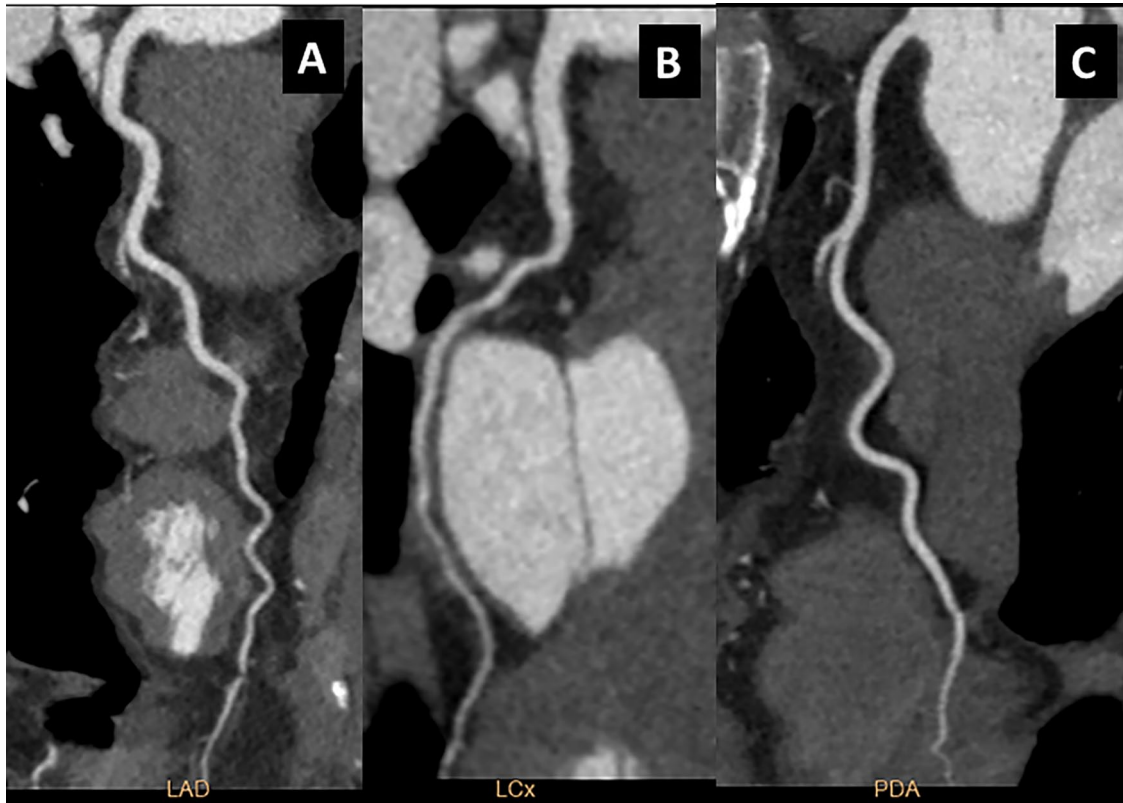


Figure 2. CT coronary angiography showing normal anatomy in right dominance and absence of significant atherosclerotic lesions: (A) left anterior descending coronary artery, (B) left circumflex coronary artery and (C) posterior descending coronary artery.

Monti drafted the imaging part of the manuscript, Luigina Guasti, Giovanni Vincenzo Gaudio and Carlo Campana contributed to drafting and final approval of the manuscript.

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