

A case series about the favorable effects of sacubitril/valsartan on anthracycline cardiomyopathy

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Abstract

Anthracyclines are the cornerstone of treatment for many solid and hematological cancers such as breast cancer or lymphoma for the past 50 years. Nevertheless, in a non-negligible proportion of patients, they elicit dilated cardiomyopathy as a side effect, which causes in turn cardiac decompensation. Conversely, for some years, sacubitril/valsartan has been proposed as a new therapeutic paradigm for all varieties of heart failure with reduced left ventricular ejection fraction, due to its balanced enhancement of natriuretic peptides' properties coupled with a blocking effect on the AT1 angiotensin receptors. In this article, two clinical cases are illustrated in which the therapeutic action of sacubitril/valsartan against anthracycline cardiomyopathy would seem to be demonstrated by the improvement of symptoms and echocardiographic parameters. Thus, further studies would be warranted for better evaluating the potential role of sacubitril/valsartan as a novel therapeutic tool against anthracycline cardiotoxicity.

Keywords

Cardiovascular, oncology, pharmacoepidemiology/drug safety, cardiac remodeling, outcome

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Introduction

In clinical practice, the cases of cardiotoxicity due to anti-neoplastic drugs have become increasingly frequent. In fact, both cytostatics and immunotherapy are used in specific cocktails that allow one to curb or block the progression of solid or hematological tumors. However, many of these therapies with an incisive anti-proliferative effect are burdened by a non-negligible risk of inducing cardiomyopathy. The modalities with which some cytostatics, in particular the compounds belonging to the anthracycline class, induce cell damage not only at the level of neoplastic clones but also at the expense of the myocardium, have been largely elucidated and brought to the knowledge of the medical community.^{1–8}

Beta blockers and angiotensin-converting enzyme (ACE) inhibitors are among the most commonly used drugs in order to prevent or attenuate the left ventricle (LV) pathological remodeling, which is chemotherapy related.^{9–12}

In addition, sacubitril/valsartan is known to exert hypotensive, natriuretic, antioxidant, and cardiac anti-apoptotic effects. These effects are due to the balanced enhancement of the physiological effects of the natriuretic peptides, both the atrial natriuretic peptide (ANP) and the B-type natriuretic

peptide (BNP), the latter being produced by the ventricular myocardium. Thus, sacubitril/valsartan amplifies and prolongs the beneficial effects of the abovementioned cardioprotective hormones by means of the inhibition of neprilysin, that is, the enzyme responsible for their degradation.¹³ In reality, the role that sacubitril/valsartan could play in the prevention and treatment of dilated cardiomyopathy secondary to anthracycline therapy has been poorly investigated so far. Thus, two cases of use of sacubitril/valsartan for the treatment of anthracycline cardiomyopathy in the context of two different types of neoplastic disease are illustrated below.

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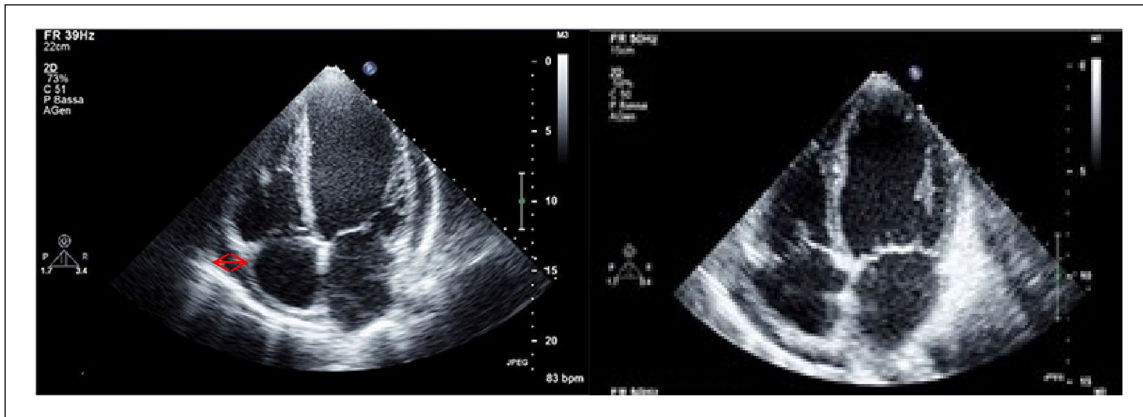


Figure 1. DS A female, 55 years. Left panel. Apical four-chamber echocardiographic view shows a moderately dilated left ventricle. In particular, at admission, normal parietal thickness, widely hypo-acinetic walls, and severely reduced overall pump function (ejection fraction 22%) were detected. In addition, the right ventricle was found to be slightly dilated and severely dysfunctional, with a slight circumferential pericardial effusion (maximum echo-free pericardial separation in diastole: 10 mm, see the red arrow). Based on clinical history, symptoms, and echocardiographic picture, the patient was diagnosed with acutely decompensated heart failure from anthracycline cardiomyopathy. This echocardiogram was made before starting therapy with sacubitril/valsartan. Right panel. The echocardiographic check after 2 weeks of therapy with sacubitril/valsartan shows a reduction in volumes of the left ventricle (indexed telediastolic volume: 90 mL/m^2), and an improvement in regional kinetics and overall systolic function (ejection fraction: 44%) (apical four-chamber view focused on the left ventricle in telesystole).

Case no. 1

The case of a 55-year-old woman treated with three ABVD cycles (adriamycin, i.e. doxorubicin (cumulative dose = 550 mg/m^2), bleomycin, vinblastine, and dacarbazine) for stage 2 Hodgkin lymphoma is described below. This therapy had been effective for the treatment of lymphocyte proliferation. However, 8 months after the last chemotherapy cycle, the patient was referred to our medical and multi-specialist center and was found to be hypertensive and affected by New York Heart Association (NYHA) Class II chronic heart failure. Transthoracic echocardiography unveiled very low left ventricular ejection fraction (LVEF) of 22%, with a slightly reduced right ventricular function (tricuspid annulus plan systolic excursion (TAPSE) = 17 mm (normal values $> 20 \text{ mm}$)), high systolic pulmonary arterial pressure of 50 mmHg, and mild pericardial effusion with anterior echo-free space of 10 mm (Figure 1). Hemodynamic invasive measurements of the right heart confirmed high filling pressures of left-sided cardiac sections and an elevated N-terminal (NT)-pro hormone BNP (NT-proBNP) of 12,678 pg/mL, with cardiac troponin I (cTnI) = 0.06 ng/mL (upper limit of normality range = 0.04 ng/mL). Therefore, the patient was diagnosed with non-ischemic dilated cardiomyopathy from anthracycline therapy. She underwent treatment with carvedilol 25 mg twice daily, enalapril 10 mg once daily, canrenone 50 mg once daily, and furosemide 40 mg depending on the symptoms. She was rigorously monitored by cardiologic team and her dosages were increased up to maximum tolerated levels. The abovementioned therapeutic scheme was kept unchanged for 4 weeks, but levels of NT-proBNP showed a continuous rise reaching a value of 15,281 pg/mL

while patient complained for dyspnea. At this point while LVEF was 22%, the patient was switched from enalapril 20 mg once daily to sacubitril/valsartan given according to the following scheme: 50 mg administered twice daily, increased after 2 weeks to 100 mg twice daily. After 2 weeks had passed, the patient reported that her dyspnea had almost completely regressed. Likewise, her NT-proBNP dropped to 7130 pg/mL with cTnI of 0.03 ng/mL. The therapy with sacubitril/valsartan was well tolerated. Furthermore, a repeat echocardiogram (Figure 1) showed an LVEF of 44%. In addition, a magnetic resonance imaging (MRI) examination was carried out 4 months after a stable titration (100 mg twice daily). It showed a normalization of LV function (LVEF of 55%) as well as a normal function of the right ventricle (RV). A further measurement of NT-proBNP documented its further fall to 1800 pg/mL. Thus, no hospitalization for worsening heart failure was required. The patient is currently managed with sacubitril/valsartan 100 mg twice daily and carvedilol 25 mg twice daily. Written informed consent was obtained from this patient for her anonymized information to be published in this article.

Case no. 2

A 65-year-old female with a history of invasive ductal carcinoma in the right breast (T1N2M1, IV stage) with esophageal metastasis was treated with specific surgery, hormone therapy (anastrozole), and TAC (docetaxel 110 mg, doxorubicin 450 mg/m^2 (cumulative dose), and cyclophosphamide 800 mg) chemotherapy.

During the first 5 months of follow-up, the patient remained symptom-free. However, following this period of

subjective well-being, the patient began complaining of worsening dyspnea and fatigue (NYHA class II).

A transthoracic echocardiogram unveiled an LVEF moderately reduced of 38%. Thus, the patient underwent therapy with ramipril 5 mg once daily, carvedilol 12.5 mg twice daily, canrenone 25 mg per day, and furosemide 25 mg depending on the presence and/or intensity of congestion symptoms. Six months later, the patient was rehospitalized due to worsening dyspnea and marked bilateral ankles' edema.

Repeated transthoracic echocardiogram led to the diagnosis of congestive heart failure with reduced left ventricular ejection fraction (HFREF). It documented an LVEF of 26% and moderate-to-severe functional mitral regurgitation. The patient was diagnosed to have a cardiomyopathy from previous anthracycline treatment. Thus, an increase in dosing for both carvedilol and ramipril was established so as to reach the maximum recommended target doses, that is, 25 mg twice daily for carvedilol and 10 mg once daily for ramipril.

Furthermore, canrenone was switched to eplerenone 25 mg per day, while furosemide was continued. After 3-month follow-up, repeated echocardiogram unveiled worsening morphovolumetric remodeling of right chambers with a mild to-moderate RV dilatation coupled with moderately impaired right ventricular function, bi-atrial enlargement, moderate functional tricuspid regurgitation, and elevated systolic pulmonary arterial pressure. NT-proBNP rose to 12,467 pg/mL with cTnI of 0.06 ng/mL; stable LVEF of 26%. Subsequently, the patient was re-directed from ramipril 10 mg per day to sacubitril/valsartan 50 mg twice daily. For the latter, at first, the up-titration was not possible, because the systolic pressure remained comprised between 90 and 100 mmHg. However, only weak dizziness arose from this initial hypotension and the patient's dosing was eventually uptitrated to 100 mg of sacubitril/valsartan given twice daily. An echocardiogram (Figure 2) showed an LVEF of 45%, normal RV with slightly reduced RV systolic function, mild bi-atrial enlargement, and systolic pulmonary arterial pressure made normal by therapy of 25 mmHg. The patient is currently managed with sacubitril/valsartan 100 mg twice daily, carvedilol 6.25 mg twice daily, and eplerenone 25 mg once daily without further heart failure re-hospitalizations in the last 24 months. Written informed consent was obtained from this patient for her anonymized information to be published in this article.

Discussion

Current guidelines recommend sacubitril/valsartan for patients with HFREF,¹⁴ but there is lack of evidence of its efficacy and safety in cancer therapy-related cardiac dysfunction (CTRCD). In fact, Scientific Societies of Cardiology have not published guidelines so far, but only position papers and expert consensus documents on management of cancer patients undergoing potentially cardiotoxic therapy.^{8,15,16} Indeed, current evidence is limited to few and very small

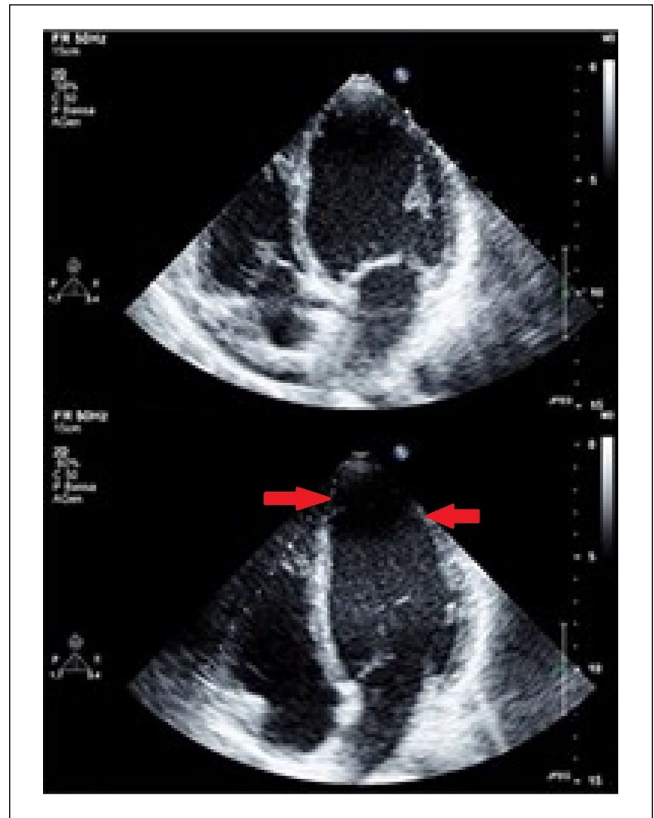


Figure 2. DE N female, 65 years. Top panel: The echocardiogram performed at the admission (top) shows severe left ventricular dilation (indexed diastolic volume 108 mL/m²), with widespread hypokinesia of the walls and severe systolic dysfunction (ejection fraction 26%). Based on clinical history, symptoms, and echocardiographic picture, the diagnosis of anthracycline cardiomyopathy was made. Bottom panel: The echocardiographic control after 2 months of therapy with sacubitril/valsartan shows an improvement in regional kinetics and global systolic function (ejection fraction 45%) (apical four-chamber view focused on the left ventricle in end-diastole). The arrow marks emphasize the improved wall kinetics after therapy with sacubitril/valsartan.

cohort studies,⁹ randomized controlled trials,¹⁰ and meta-analyses,^{11,12} which would support the effectiveness of beta-blockers and ACE inhibitors (ACE-i) on preservation or improvement of LV function following chemotherapy-related cardiomyopathy.

However, a retrospective cohort study was recently performed to analyze the potential benefit of sacubitril/valsartan in patients with CTRCD.¹⁷ In this study, baseline NT-proBNP levels (1552 pg/mL (692; 3624) versus 776 (339; 1458)), functional class (2.2 ± 0.6 versus 1.6 ± 0.6), and LVEF (33% (27; 37) versus 42% (35; 50)) improved at the end of follow-up (all p-values ≤ 0.01). Biochemical, clinical, and echocardiographic improvements were found regardless of the achieved sacubitril-valsartan dose (low or medium/high doses).¹⁷

Outside of this observational study, there are currently no exhaustive data on the subject, at most you can find anecdotal

reports¹⁸ or reports on the experimental application of the drug to investigational animal models of doxorubicin-induced cardiotoxicity.¹⁹

In this context characterized by a lack of guidelines concerning the use of sacubitril/valsartan in heart failure arisen in cancer patients, our contribution seems to be useful to us. In fact, two cases of anthracycline cardiomyopathy are represented which appear to receive tangible benefits by the addition of sacubitril/valsartan to the therapy. In fact, echocardiographic measures, in particular LVEF, as well as the NYHA class, appear improved by the drug in the short term. Nevertheless, the inferences about the improved clinical and echocardiographic picture consequent to use of sacubitril/valsartan for anthracycline cardiomyopathy must be confirmed by well thought out murine experimental models devoted to the assessment of the effects of sacubitril/valsartan compared to conventional therapy in mice with anthracycline-induced cardiomyopathy. In addition, the very exiguous sample size, that is, only two cases do not allow conclusive and adequately documented deductions about the alleged property of sacubitril/valsartan of efficaciously antagonizing the anthracycline-induced myocardial damage.

Conclusion

Sacubitril/valsartan, that is, the progenitor of the new pharmacological class termed “angiotensin receptor and neprilisin inhibitors” (ARNI), would seem to be able to antagonize the unfavorable remodeling of the LV induced by anthracyclines. This action is confirmed by the inferences that arise from the two cases reported, in which a therapeutic action of sacubitril/valsartan against anthracycline cardiomyopathy appears to be proven by the improvement of symptoms and echocardiographic parameters. It being understood that only two responders to sacubitril/valsartan therapy are a sample too small with regard to the objective of realizing a well-documented evidence able to warrant a randomized controlled trial, however, such a kind of study would be welcome in future in order to ascertain in a more reliable way the efficacy and safety of sacubitril/valsartan for anthracycline cardiomyopathy.

Author contributions

Both the author contributed to the study conception and design, acquisition of data, analysis and interpretation of data, drafting of the article, and critical revision.

Availability of data and materials

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Consent to participate

Both patients, whose clinical descriptions constitute the subject of this article, gave informed consent to participate in the study, provided that anonymity was rigorously preserved

Declaration of conflicting interests

The author(s) Renato De Vecchis and Andrea Paccone, have no competing interests concerning the content of this article.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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