Successful treatment of doxorubicin-induced cardiomyopathy with low-dose sacubitril/valsartan: a case report

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Background Cancer therapy–related cardiac dysfunction (CTRCD) is a challenging and life-threatening complication of many chemotherapeutic regimens. CTRCD prevention, diagnosis, and therapy require both careful interdisciplinary assessment and management. For patients with CTRCD, current guidelines of the European Society of Cardiology (ESC) recommend an angiotensin-converting-enzyme inhibitor in combination with a beta-blocker. Recent studies indicate a beneficial effect of sacubitril/valsartan in this patient population.

Case summary A 68-year-old female patient with a pleural epithelioid angiosarcoma developed heart failure with reduced ejection fraction and elevated serum biomarkers following doxorubicin treatment. After implementation of a recommended cardioprotective medical therapy including torasemide, ramipril, carvedilol, and spironolactone, the patient suffered two cardiac decompensations within 4 weeks after initiation of a paclitaxel regimen and pleural radiation therapy due to pain exacerbation. Despite a continuous application of the cardioprotective medical treatment regimen, no improvement of left-ventricular ejection fraction (LVEF) was detected in a 4-month follow up. Interestingly, after omitting ramipril and implementing low-dose sacubitril/valsartan (26/24 mg), we observed a decrease in serum biomarkers within 3 months as well as a significant improvement of LVEF within 6 months. After nearly 10 months of disease stabilization under paclitaxel, the patient suffered progressive cancer disease and deceased 1 week later after the initiation of a therapeutic attempt with pazopanib.

Discussion This case report highlights the importance of interdisciplinary care in cancer patients as well as the promising role of (low-dose) sacubitril/valsartan in patients with CTRCD even in the setting of delayed initiation.

Keywords Cardiotoxicity • Cardio-oncology • Sacubitril/valsartan • Case report • Cardiovascular imaging • Doxorubicin

ESC Curriculum 6.9 Cardiac dysfunction in oncology patients • 6.2 Heart failure with reduced ejection fraction • 2.3 Cardiac magnetic resonance • 2.2 Echocardiography
Learning points

- CTRCD is a frequent and challenging complication of several cancer therapies.
- An interdisciplinary management, preferably within a joint cardio-oncological service, is vital for prevention, early diagnosis, treatment, and outcome.
- Sacubitril/valsartan in low and standard doses is a promising therapeutic approach in CTRCD which might have the potential to improve cardiac function even in the setting of delayed therapy initiation.

Introduction

Cancer therapy–related cardiac dysfunction (CTRCD) is a frequent complication of many chemotherapeutic regimens with varying occurrence.\(^1\) In a recently published prospective registry analysis the overall prevalence of anticancer therapy-induced cardiotoxicity was found to be as high as 37.5%.\(^2\) CTRCD is usually described as a decrease in left-ventricular ejection fraction (LVEF) to below 50% or a decrease from baseline of >10% below the lower normal limit.\(^3\) Development of CTRCD depends on a variety of patient- and therapy-related factors.\(^4\) CTRCD prevention requires attentive risk assessment as well as surveillance and management before, during, and after application of potential cardiotoxic substances. An interdisciplinary cardio-oncological approach is recommended, especially in high-risk patients.\(^6\) For patients developing left-ventricular (LV) dysfunction following chemotherapy, current guidelines of the European Society of Cardiology (ESC) for the diagnosis and treatment of acute and chronic heart failure recommend treatment with an angiotensin-converting enzyme inhibitor (ACE-I) and a beta-blocker (BB), preferably carvedilol.\(^6\) Interestingly, recent studies indicate that sacubitril/valsartan is a beneficial therapeutic approach with significant improvement of clinical symptoms as well as laboratory and imaging parameters in patients with CTRCD.\(^5–8\)

Case presentation

A 68-year-old female without significant medical history aside from arterial hypertension was admitted to our hospital for treatment of a pleural epithelioid angiosarcoma (Stage IV). Due to inoperability and severe encephalopathy complicating therapy with ifosfamide, an initial neoadjuvant regimen with doxorubicin/ifosfamide was altered into a palliative regimen of doxorubicin alone for a total of seven cycles (cumulative dose: 420 mg/m²). Dexrazoxane was administered for cardioprotective reasons during the last two cycles. Initial transthoracic echocardiographic examination documented a LVEF of 65% (see Supplementary material online, Video S1) as well as a normal global longitudinal strain (GLS; −19.8%). However, 4 months later, a significant decline of LVEF from 65 to 40%, as well as a decline of GLS to −10.4% was documented in an outpatient clinic. Additionally, elevated serum levels of BNP (reference value <100 pg/mL) and hs-TNI were observed. The first documented LVEF deterioration became evident in 05/20, 3 months after last administration of doxorubicin, and was in line with increased brain natriuretic peptide (BNP, reference value <100 pg/mL) and high-sensitive troponin I (hs-TNI, reference value <24 mg/mL) levels. An initial guideline-directed medical therapy (GDMT) proved ineffective. After implementing sacubitril/valsartan in 11/20, we could observe lowered levels of serum biomarkers (02/21) as well as an improved LVEF (06/21). The patient deceased a week after pazopanib initiation. cd, cumulative dose.

Timeline

The first documented LVEF deterioration became evident in 05/20, 3 months after last administration of doxorubicin, and was in line with increased brain natriuretic peptide (BNP, reference value <100 pg/mL) and high-sensitive troponin I (hs-TNI, reference value <24 mg/mL) levels. An initial guideline-directed medical therapy (GDMT) proved ineffective. After implementing sacubitril/valsartan in 11/20, we could observe lowered levels of serum biomarkers (02/21) as well as an improved LVEF (06/21). The patient deceased a week after pazopanib initiation. cd, cumulative dose.
(reference value <24 mg/mL) were detected. Symptoms of heart failure were not reliably distinguishable from symptoms of the underlying tumour disease accompanied by a hyporegenerative macrocytic anaemia necessitating transfusion of blood substituents. However, at this point, no heart failure medication was initiated. Six weeks after first diagnosis of heart failure with reduced ejection fraction (HFrEF), the patient was admitted to our cardio-oncological department for the first time. At presentation, the patient solely complained about a slightly decreased exercise capacity. Neither shortness of breath nor angina pectoris. Cardiovascular examination and assessment of vital signs were unremarkable. Moreover, electrocardiography (ECG) showed no relevant abnormalities aside from a first-degree atrioventricular block. For further evaluation of the underlying aetiology of HFrEF, we performed cardiac magnetic resonance imaging (cMRI) which revealed a progressive deterioration of LVEF to 17%, most likely attributable to cardiotoxicity (Figure 1, supplementary material available online). Subsequent echocardiographic examination confirmed this finding (see Supplementary material online, Video S2). Late gadolinium enhancement imaging was unremarkable. A GDMT in accordance with the then valid international guidelines and expert recommendations was immediately initiated, including torasemide (5 mg QD), ramipril (2.5 mg QD), carvedilol (6.25 mg BD), and spironolactone (12.5 mg QD); later ivabradine (2.5 mg BD) was added. At the same time, progressive cancer disease led to a severe pain exacerbation. The patient received radiation therapy of the pleura as well as a palliative regimen of paclitaxel for a total of eight cycles over the next 10 months. Unfortunately, it proved difficult to execute a complete GDMT due to repeated symptomatic hypotension and two cardiac decompensations within 4 weeks after radiation and initiation of paclitaxel. Four months after implementation of GDMT, no improvement of LVEF and serum biomarkers was found. Therefore, we stopped ramipril therapy and initiated treatment with sacubitril/valsartan. However, due to currently low blood pressure values, an increase in the dosage was not possible and the patient continuously received a low-dose regimen (i.e. 26/24 mg BD). Thereafter, a decrease in serum BNP and hs-TNI levels could be observed within 3 months’ time, and a significant improvement of LVEF to approximately 50% (see Supplementary material online, Video S3) as well as an improved GLS (−17.3%) could be assessed another 3 months later. On the basis of considerable progressive disease after 10 months of paclitaxel treatment, after careful consideration, and without a reasonable alternative, a low-dose therapeutic attempt with pazopanib was undertaken. However, the patient

Figure 1  Cardiac magnetic resonance imaging demonstrating dilatation of both ventricles as well as a highly reduced left-ventricular ejection fraction of 17% left-ventricular end-diastolic volume: 187 mL, left-ventricular end-systolic volume: 156 mL. (A) Four-chamber view, diastole. (B) Four-chamber view, systole. (C) Short-axis view, diastole. (D) Short-axis view, systole.
and varying incidences (up to 48% for doxorubicin, 7–11% for pazopanib, life-limiting complication of many chemotherapeutic regimens with a high risk of death remaining uncertain. Therefore, a thorough risk assessment before initiation of an oncological treatment regimen as well as regular follow-up visits in an interdisciplinary cardio-oncological department are mandatory to enable early detection of potential cardiotoxicity and provide appropriate and timely cardioprotective therapy. Sacubitril/valsartan is a promising therapeutic option for patients with CTRCD even in those with a delayed diagnosis, which constitutes a scientific novelty. Further basic and clinical research is necessary to confirm the beneficial effect of low- and standard-dose sacubitril/valsartan in this particular patient population.

Discussion

We report a case of CTRCD due to doxorubicin application responding well to low-dose sacubitril/valsartan. CTRCD is a frequent as well as life-limiting complication of many chemotherapeutic regimens with varying incidences (up to 48% for doxorubicin, 7–11% for pazopanib, and <1% for paclitaxel). Risk assessment and risk-dependent monitoring must include a thorough medical history, ECG, natriuretic peptides, troponin, and a comprehensive transthoracic echocardiography (TTE). In addition, GLS should be regularly conducted as it has shown the potential to detect subclinical and therefore early cardiac dysfunction due to cardiotoxicity. The current position statement of the Heart Failure Association, the European Association of Cardiovascular Imaging, and the Cardio-Oncology Council of the ESC proposes useful tools for risk assessment depending on the applied chemotherapeutic regimen. According to this position statement, our patient who provided the risk factors age, arterial hypertension, and doxorubicin dose >400 mg/m², was at high risk for developing cardiotoxicity. For high-risk patients, follow-up intervals of serum biomarkers and TTE including GLS are recommended every two cycles of chemotherapy as well as 3–6 and 12 months after completion of the last cycle. Early detection of cardiac dysfunction is mandatory, as reversibility of cardiac dysfunction has been shown to be inversely proportional to the time interval from the last application of chemotherapy to the beginning of heart failure therapy. Since a complete recovery can only be expected after therapy initiation within the first 6 months after onset of CTRCD, timely diagnosis is of highest importance. One might hypothesize that an earlier presentation of the patient in our cardio-oncological department would have led to an earlier detection of (subclinical) cardiac dysfunction, and subsequent timely initiation of cardioprotective medication could have prevented development of HFpEF.

As previously described, medical therapy with an ACE-I combined with a BB is recommended in patients with CTRCD according to the latest ESC guidelines. Although sacubitril/valsartan has been proved to be a game changer in the treatment of patients with HFpEF, its role in CTRCD still remains elusive with published data mostly derived from case reports or small scale studies. In 2020, two independent groups published three studies indicating a beneficial effect of sacubitril/valsartan in CTRCD patients. Thus, the application of sacubitril/valsartan resulted in an improvement of the New York Heart Association functional class, myocardial function, and serum N-terminal prohormone of BNP levels. These improvements were also observed at lower doses of sacubitril/valsartan, consistent with the findings of our case study. Remarkably, in the case presented here, sacubitril/valsartan was initiated at a point at which LVEF recovery has been shown to be highly unlikely in patients with CTRCD. Our findings therefore emphasize the therapeutic value of sacubitril/valsartan in patients with CTRCD. While additional randomized controlled trials with a larger number of patients are needed, the evidence strongly suggests that sacubitril/valsartan in low and standard doses is a well-tolerated, efficient, and safe therapeutic option for CTRCD treatment.

Conclusion

Management of cancer patients with CTRCD continues to be challenging. Therefore, a thorough risk assessment before initiation of an oncological treatment regimen as well as regular follow-up visits in an interdisciplinary cardio-oncological department are mandatory to

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: S.G. has received honoraria for consulting from AstraZeneca and honoraria for lectures from Boehringer Ingelheim, Pfizer, Bayer Healthcare, and ZOLL. S.K. has received honoraria for consulting from ALMIRAL not associated with this work. A.D. and E.B. have nothing to declare.

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