

CASE REPORT

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Add-on multidrug treatment based on quadruple therapy successfully treated worsening heart failure caused by anthracycline-induced cardiomyopathy in a survivor of cancer as a young adult: a case report

Hiroataka Oda^{1*}, Yuka Hayashi¹, Norihito Oyanagi¹, Komei Tanaka¹, Kazuyuki Ozaki¹, Asami Kashiwa¹, Yukio Hosaka¹, Keiichi Tsuchida¹ and Kazuyoshi Takahashi¹

Abstract

Background The overall mortality and morbidity benefit in patients with heart failure with a reduced ejection fraction is greatest with a treatment combination of sacubitril/valsartan, beta-blockers, mineralocorticoid-receptor antagonists, and sodium-glucose transporter-2 inhibitors, termed the “fantastic four” or “quadruple therapy.” The addition of vericiguat (an oral soluble guanylate cyclase stimulator) is believed to aid in managing worsening heart failure after quadruple therapy. Among childhood and young adult cancer survivors, cardiovascular complications that develop more than 10 years after anthracycline-based chemotherapy have a poor prognosis. Therefore, this study reports the efficacy of multidrug regimen based on quadruple therapy for worsening heart failure in cancer survivors with anthracycline-induced cardiomyopathy.

Case presentation A survivor of cancer as a young adult who received high-dose anthracycline chemotherapy presented with acute decompensated heart failure 20 years post-chemotherapy and worsening heart failure 1.5 years after discharge. The patient showed signs of improvement after a step-wise introduction of carvedilol, empagliflozin, sacubitril/valsartan, ivabradine, and spironolactone for worsening heart failure. Vericiguat was accelerated owing to the risk of more severe cardiovascular events associated with ongoing aortic stenosis and the poor prognosis of anthracycline-induced cardiomyopathy. Heart failure symptoms continued to improve, with significant cardiac reverse remodeling, and the patient successfully underwent aortic valve replacement for severe aortic stenosis.

Conclusions Our case highlighted that multidrug treatment with add-on vericiguat and ivabradine based on quadruple therapy can potentially treat worsening heart failure in young adult cancer survivors with severe anthracycline-induced cardiomyopathy.

*Correspondence:

Hiroataka Oda
hirooda202004@gmail.com

Full list of author information is available at the end of the article



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Keywords Anthracycline-induced cardiomyopathy, Cancer survivor, Cardiac reverse remodeling, Worsening heart failure, Vericiguat, Aortic stenosis, Quadruple therapy, Case report

Background

Treatment advancements have improved the prognoses of patients with cancer, with more than half surviving longer than 10 years [1]. Child, adolescent, and young adult cancer survivors have a poor prognosis if cardiovascular complications develop more than 10 years post-treatment, as these complications are the leading cause of mortality among cancer survivors [2, 3]. Cancer survivors with anthracycline (ATC)-induced cancer treatment-related cardiac dysfunction (CTRCD) also have a poor prognosis [4, 5]. Current guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) includes four drug classes: renin-angiotensin system inhibitors (RASi), beta-blockers (BBs), mineralocorticoid-receptor antagonists, and sodium-glucose transporter-2 inhibitors. Additionally, a combination of these drugs using sacubitril/valsartan as RASi, known as the “fantastic four” or “quadruple therapy,” has demonstrated clinical benefit, with a 61% relative risk reduction in all-cause mortality [6, 7].

This case report discusses the potential efficacy of a multidrug treatment based on quadruple therapy, with the addition of vericiguat and ivabradine, for managing worsening heart failure (WHF) in young adult cancer survivors, as observed in a case of severe anthracycline-induced cardiomyopathy.

Case presentation

A 69-year-old female had received antihypertensive drugs (azilsartan [20 mg/day] and amlodipine [10 mg/day]) for over 15 years. The patient previously had non-Hodgkin's lymphoma (stage IV) and underwent repeated courses of chemotherapy for each relapse between the ages of 35–49 years, resulting in complete remission (chemotherapy drug/cumulative dose [mg/m²]: doxorubicin [DOX]/218; pirarubicin/830; mitoxantrone/33; cyclophosphamide/23,758; vincristine/72; etoposide/333; and carboplatin/85; and rituximab/1,358; the equivalent DOX dose to assess ATC cardiotoxicity was 691 mg/m²). Furthermore, the patient received endoscopic submucosal dissection for early-stage rectal cancer and a right hemicolectomy for colon cancer at the age of 65 years.

The patient subsequently presented with exertional dyspnea and abdominal distention and was hospitalized for acute HF in August X, 1.5 months after symptom onset (this admission date was considered the reference date). Figure 1 describes the treatment course

and examination results. Upon admission, the patient was in clinical scenario 2, with chest X-ray (CXR) findings of a pleural effusion, cardiac enlargement, and moderate pulmonary congestion (CXR2 in Fig. 1). An electrocardiogram (ECG) revealed sinus tachycardia (E2 in Fig. 2). A systolic murmur was heard, suggesting aortic stenosis (AS). Initial oxygen and intravenous diuretic therapies relieved the HF symptoms. Azilsartan was titrated to 40 mg/day, and azosemide (30 mg/day) and carvedilol (5 mg/day) were added early in the treatment course. A two-dimensional echocardiogram (2DE) revealed left ventricular (LV) and left atrial (LA) enlargement, reduced left ventricular wall motion (LVWM) with an 18% left ventricular ejection fraction (LVEF), and an elevated tricuspid regurgitant maximum pressure gradient (TRmaxPG) of 41 mmHg. All three calcified aortic valve leaflets had restricted openings, with a 30-mmHg aortic valve pressure gradient (AVPG) (#1 in Table 1). Dobutamine Stress 2DE ruled out severe AS. Computed tomography (CT) revealed an aortic valve calcium score of 1,189 Agatston units (AU). Coronary angiography (CAG) demonstrated no significant stenosis. Cardiac catheterization revealed increased pulmonary artery wedge pressure, increased LV end-diastolic pressure, pulmonary hypertension (PH), decreased cardiac output index, and low AVPG. Brain natriuretic peptide (BNP) levels declined from 1,183 pg/mL at admission to 710 pg/mL at discharge. In January X + 1, five months after reference date and four months post-discharge, weight gain was observed, and the BNP level increased to 2,986 pg/mL, indicating WHF. Azosemide was titrated to 45 mg/day, slow-release nifedipine at 20 mg/day was added to control blood pressure below 120 mmHg, and carvedilol was titrated to 7.5 mg/day. The patient remained stable at New York Heart Association (NYHA) class 2, with BNP levels of 1,100–1,900 pg/mL over the following year.

In March X + 2, one year and seven months after the reference date, the patient was suspected of having WHF with possible progression toward severe AS. This suspicion was based on an ECG in February X + 2 (one year and six months after the reference date) demonstrating LV strain (E4 in Fig. 2) and a CXR in March X + 2 (one year and seven months after the reference date) demonstrating cardiac enlargement (CXR4 in Fig. 1). Azilsartan was substituted with empagliflozin at 10 mg/day and sacubitril/valsartan at 200 mg/day (titrated to 400 mg/day over four weeks). Approximately

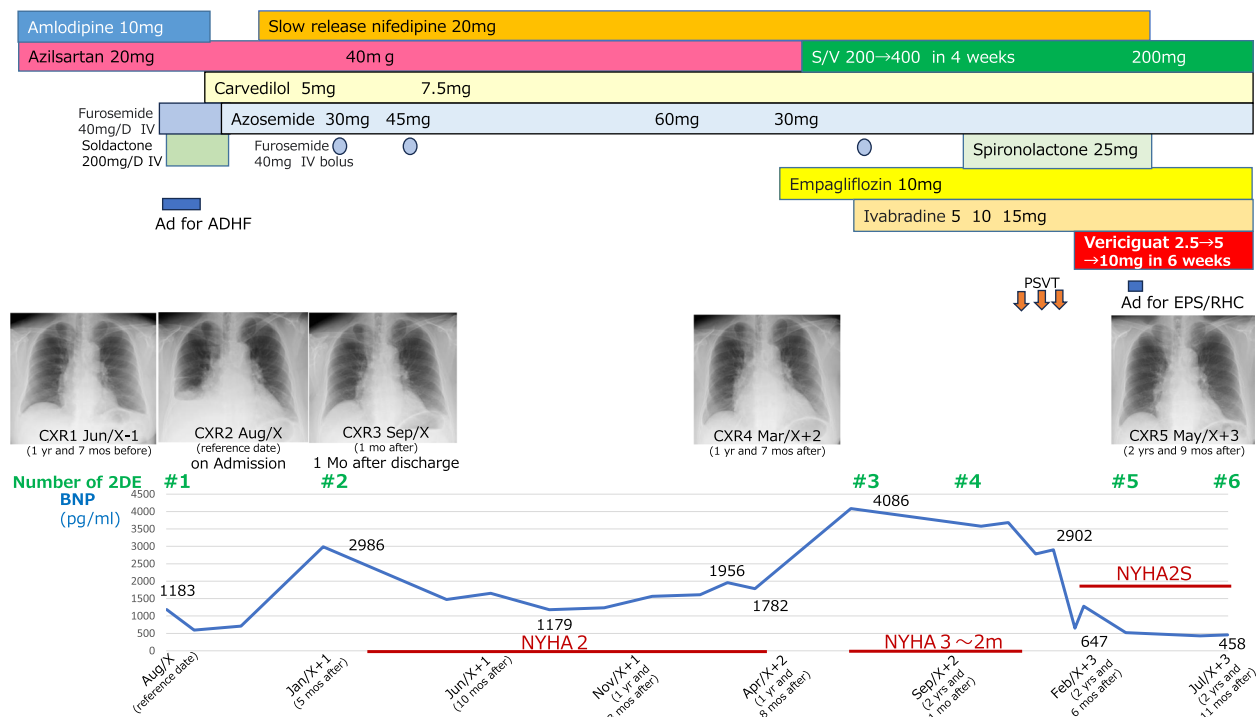


Fig. 1 Treatment and examination timeline with results. The number of 2DE indicates the number of two-dimensional echocardiograms, and numbers 1–6 correspond to those in Table 1. The admission date of August X is considered the reference date. Ad, admission; ADHF, acute decompensated HF; BNP, brain natriuretic peptide; CXR, chest X-ray; D, day; EPS, electrophysiological study; IV, intravenous administration; NYHA, New York Heart Association; NYHA2m, NYHA class II moderate limitation of physical activity; NYHA2S, NYHA class II with a slight limitation of physical activity; PSVT, Paroxysmal supraventricular tachycardia; RHC, right heart catheterization; S/V, sacubitril/valsartan; 2DE, two-dimensional echocardiogram

three months later (one year and 11 months after the reference date), the patient rapidly experienced WHF symptoms, including dyspnea and abdominal distention, classified as NYHA class III. The symptom progression coincided with physical exertion, as the patient's partner had undergone surgery and required care. Ivabradine was added to achieve heart rate control between 50–60 bpm, and a diuretic was used as needed to achieve target morning weight maintenance. Cardiac status subsequently improved to NYHA class II moderate limitation of physical activity (NYHA class II_m). The 2DE in October (two years and two months after the reference date) revealed a slight decrease in LV systolic dimension, slight LVEF improvement to 29%, and AS progression (#4 in Table 1). Therefore, spironolactone at 25 mg/day was started as quadruple therapy. BNP levels decreased to 2,902 pg/mL in early February X+3 (two years and six months after the reference date). Vericiguat was started in late February after receiving quadruple therapy and ivabradine treatment, without a 2DE evaluation. HF symptoms improved with weight loss owing to increased urine output, and the BNP level decreased below 650 pg/dL. The 2DE in March X+3

(two years and seven months after the reference date) revealed the same LVEF and AVPG as in October X+2 (two years and two months after the reference date), in addition to decreasing LV dimensions and a normalized TRmaxPG (#5 in Table 1). Paroxysmal supraventricular tachycardia with hypotension frequently occurred, and the patient was readmitted in June (two years and 10 months after the reference date) for an electrophysiological study and right heart catheterization (RHC). RHC revealed mild PH, and right ventricular myocardial biopsies demonstrated drug-induced myocardial damage: the cardiomyocyte diameter was mildly enlarged, with noticeable anisokaryosis of the cardiomyocyte nuclei, some cardiomyocytes exhibited giant nuclei, and cytoplasmic vacuolar degeneration was observed. Mallory staining revealed fibrosis unrelated to the vascular structure between the cardiomyocytes, with the replacement of the myocardium by fibrous tissue. The 2DE in June (two years and 10 months after the reference date) revealed normalized LV diameter, a moderate reduction in LA enlargement, improved LVWM (52% LVEF), and a normalized TRmaxPG; however, the AVPG increased to 77 mmHg, with a Vmax

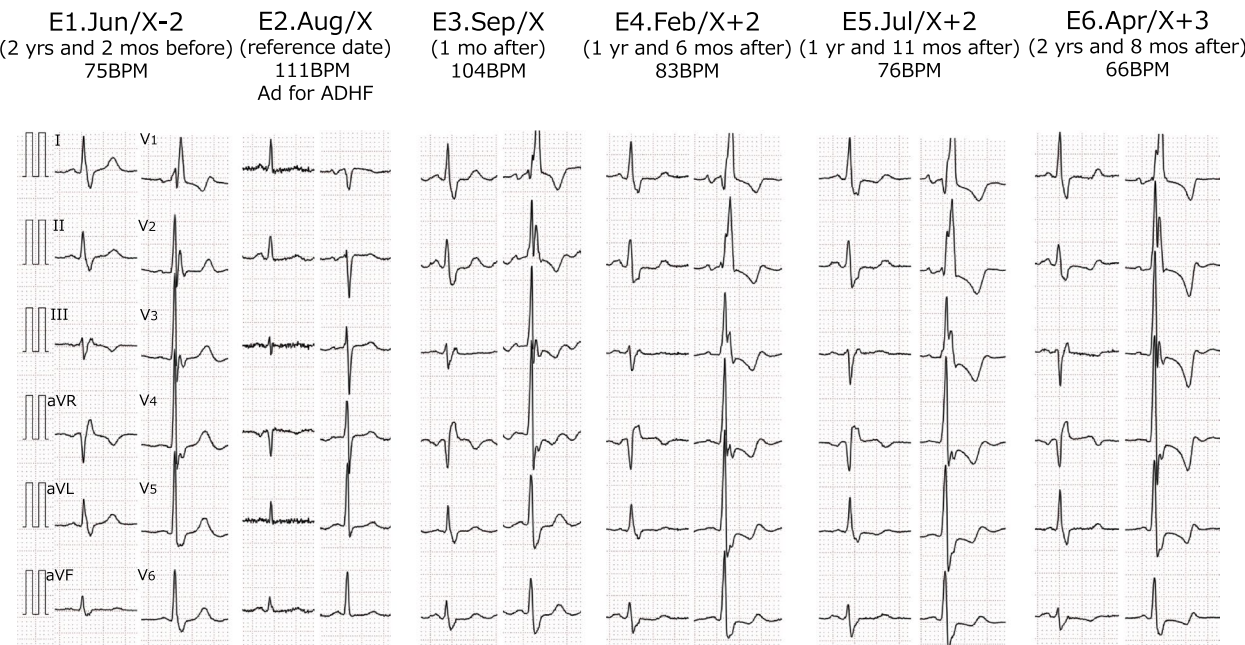


Fig. 2 Electrocardiogram changes over time. E1.Jun/X-2: one year and two months before ADHF; E2.Aug/X (reference date): Upon admission for ADHF; E3.Sep/X: one month after ADHF; E4.Feb/X + 2 (1 year and 6 months after the reference date): 1.5 years after discharge, a left ventricular strain pattern appeared, and the second WHF episode was imminent; E5.Jul/X + 2 (1 year and 11 months after the reference date): During the second WHF episode; E6.Apr/X + 3 (2 years and 8 months after the reference date): A period of significant cardiac reverse remodeling. The admission date of August X is considered the reference date. Ad, admission; ADHF, acute decompensated heart failure; BPM, beats per minute; TP, therapy; WHF, worsening heart failure

Table 1 Dynamic trajectory of echocardiographic findings and medication with cardiac reverse remodeling

2DE	#1Aug/X (reference date)	#2Jan/X + 1 (5 mos after)	#3Jul/X + 2 (1 yr and 11 mos after)	#4Oct/X + 2 (2 yrs and 2 mos after)	#5Mar/X + 3 (2 yrs and 7 mos after)	#6Jun/X + 3 (2 yrs and 10 mos after)
LVDD(mm)	59	61	60	60	58	55
LVSD(mm)	54	54	54	51	50	40
LVEF(%)	18	22	22	29	30	52
LA(mm)	58	52	53	54	47	47
E/A ratio	2.5	2.7	4.3	2.3	0.5	0.6
TRmaxGP(mmHg)	41	50	35	35	16	12
AVPG(mmHg)	30	32	40	66	63	77
Numbers of drugs with CRR	1	2	3	4	6	5
Drugs	ARB	ARB, BB	S/V, BB, SGLT2i	S/V, BB, SGLT2i, Iba	S/V, BB, SGLT2i, Iba, MRA, Veri	S/V, BB, SGLT2i, Iba, Veri

LVDD and LVSD decrease started on #5Mar/X + 3 (2 years and 7 months after the reference date), LVEF increase started on #4Oct/X + 2 (2 years and 2 months after the reference date), and the TRmaxPG decreases to normal range on #5Mar/X + 3 (2 years and 7 months after the reference date). AVPG increased from #4Oct/X + 2 (2 years and 2 months after the reference date). The admission date of August X is considered the reference date

The numbers of the two-dimensional echocardiograms 1–6 correspond to those described in Fig. 1

ARB angiotensin receptor blocker, BB beta-blocker, CRR cardiac reverse remodeling, AVPG aortic valve pressure gradient, Iba ivabradine, LA left atrium, LVDD left ventricular diastolic dimension, LVEF left ventricular ejection fraction, LVSD left ventricular systolic dimension, MRA mineralocorticoid-receptor antagonist, S/V sacubitril/valsartan, SGLT2i sodium-glucose transporter-2 inhibitor, TRmaxPG tricuspid regurgitant maximum pressure gradient, Veri vericiguat

of 4.4 m/s and aortic valve orifice area of 0.55 cm², which was diagnosed as severe AS (#6 in Table 1). The restricted openings of all calcified aortic valve leaflets were unchanged; however, all leaflets appeared slightly thickened and brightened. CT revealed that the aortic valve calcium score increased to 2,468 AU. Amlodipine was discontinued, and sacubitril/valsartan was tapered to mid-dose owing to persistent hypotensive symptoms. Spironolactone was discontinued due to hyperkalemia. The patient was stable at NYHA class II with a slight limitation of physical activity (NYHA class IIs) on sacubitril/valsartan at 200 mg/day, empagliflozin at 10 mg/day, carvedilol at 7.5 mg/day, azosemide at 30 mg/day, ivabradine at 15 mg/day, and vericiguat at 10 mg/day. An aortic valve replacement (AVR) for severe AS was successfully performed in September (three years and one month after the reference date), with good subsequent clinical outcomes.

Discussion and conclusions

This report describes an adult who survived cancer as a young adult but had risk factors for increased cardiac dysfunction (high-dose ATC chemotherapy and post-exposure hypertension) and experienced acute HF 20 years post-chemotherapy, along with two WHF episodes post-discharge [2]. The onset of the second episode of WHF symptoms occurred during quadruple therapy induction, necessitating ivabradine initiation. The patient improved to NYHA class IIm with a trend of decreasing BNP levels due to the five-drug combination. However, the sixth HF drug, vericiguat, was introduced six weeks after starting the five-drug combination due to the increased risks of severe cardiovascular events associated with ongoing AS requiring imminent invasive therapy, as well as the poor prognosis of ATC-induced cardiomyopathy, with a five-year survival rate of <50% after the onset of symptomatic HF [8]. The multidrug combination therapy improved the WHF with ATC-induced cardiomyopathy, and the patient uneventfully survived AVR and showed significant cardiac reverse remodeling (CRR).

ATC-based chemotherapy is associated with irreversible dose-dependent cardiac damage. The specific mechanisms of ATC cardiotoxicity remain unclear; however, the major cellular targets are cardiomyocytes, among others, such as cardiac progenitor cells, cardiac fibroblasts, endothelial cells, smooth muscle cells, endothelial progenitor cells, and mesenchymal stromal cells. The main pathophysiological mechanisms include oxidative stress, DNA damage, senescence, and cell death, with potentially different effects and degrees of involvement in different cell types [9, 10]. The patient developed colon and rectal cancer after chemotherapy, and the initial 2DE during the first hospitalization revealed significant aortic valve

sclerosis relative to the patient's age. Considering this, the senescence-associated secretory phenotype associated with ATC may have played a role as the hinge between cancer and cardiovascular disease induced by senescent cardiovascular cells [11]. Furthermore, hypertension requiring antihypertensive drugs occurred less than five years after chemotherapy treatment, suggesting a potential association with this phenomenon. ATC cardiotoxicity is potentially a continuous phenomenon, beginning at the myocardial cell level, followed by progressive functional decline (asymptomatic cardiotoxicity in months) and overt HF (symptomatic cardiotoxicity in years), all manifesting as different evolutionary stages of the same phenomenon. The time to onset of symptomatic HFrEF varies among patients [10], indicating that the activation of cardiac compensatory mechanisms, including survival factors, typically delays symptomatic cardiac dysfunction for years. However, cardiac function progressively declines several years to more than 10 years after chemotherapy due to the exhaustion of compensatory mechanisms and the onset of additional stressors, such as hypertension and coronary artery disease, eventually leading to a symptomatic state [12]. One factor delaying overt HF in our patient was the use of angiotensin receptor blockers (ARB) for hypertension, which concomitantly acted as HF therapy. The patient's blood pressure, which was not controlled based on contemporary hypertension guidelines, atherosclerotic AS, and aging constituted additional stressors. Consequently, the collapse of cardiac compensatory mechanisms caused acute HF 20 years post-chemotherapy.

The VICTORIA trial, a double-blind, randomized, controlled trial comparing vericiguat to placebo in patients with a history of GDMT use and severe HFrEF, including those with WHF, demonstrated the clinical benefit of vericiguat for reducing cardiovascular death or HF hospitalization, without severe adverse effects [13]. Intracellular cyclic guanosine monophosphate (cGMP) levels are decreased in patients with HF, and increased cGMP levels inhibit cardiac remodeling, vascular injury, fibrosis, and inflammation. This increase in cGMP results from the nitric oxide (NO)-soluble guanylyl cyclase (GC)-cGMP signaling pathway stimulated by vericiguat and the natriuretic peptide-particulate GC-cGMP signaling pathway triggered by sacubitril/valsartan in different compartments [14]. Therefore, future clinical trials should investigate the clinical efficacy of combining these two drugs in HFrEF. Additionally, vericiguat directly stimulates soluble GC (sGC) in a NO-independent manner and enhances the sensitivity of sGC to endogenous NO, which may be effective in HF due to atherosclerosis with impaired endothelial function, such as in this case. Animal experiments have shown that sGC activity decreases

in DOX-mediated cardiomyopathy, and this reduced activity exacerbates reactive oxygen species generation and cardiac dysfunction [15]. This reduced sGC activity is permanent; therefore, activating sGC is considered to have therapeutic potential in treating symptomatic ATC-induced CTRCD.

Recent recommendations suggest quadruple therapy as the standard of care in WHF, prioritizing rapid sequence or simultaneous initiation of key agents rather than escalating their doses. Furthermore, early up-front vericiguat use is recommended for patients with WHF alongside quadruple therapy, as tolerated, to further reduce the risk of residual adverse clinical outcomes [16]. Based on our experience with vericiguat use, we formulated the following policy regarding the timing of adding this drug. Early initiation of vericiguat in WHF should be based on an individualized residual risk assessment. Even if clinical symptoms remain stable with quadruple therapy, vericiguat should be initiated under the following conditions: when there is a high likelihood of future adverse events due to, such as in this case, ongoing AS or ACT-induced cardiomyopathy with a poor prognosis. Vericiguat should also be initiated when the decrease in BNP or N-terminal pro-BNP (NT-proBNP) levels is unacceptable (a reduction rate of 30% or less) [17, 18], or when the LVEF has not recovered to baseline or remains less than 50% after approximately three months.

CRR is a surrogate measure for HFrEF improvement, which is an important goal in HFrEF treatment. BBs are known to achieve the highest CRR, with gradual dose increases recommended while monitoring for HF or bradycardia occurrence. According to the package insert for the carvedilol used in this case in Japan, the dosage starts at 1.25 mg two times daily, and the dose is gradually increased at intervals of at least one week, if tolerated, with a maintenance dose of 2.5–10 mg two times daily. This is considerably lower than the dosages in package inserts from Western countries. Specifically, this is because clinical trials conducted in Japan have confirmed sufficient efficacy of BBs, even at low doses, and fewer side effects have been observed. This background relates to the fact that WHF and intolerance were frequently observed in the early stages of BB introduction in Japan. In our case, up-titration of carvedilol was halted at 7.5 mg/day, during which BNP levels ranged between 1,100–1,900 pg/mL, and clinical inertia may have occurred due to concerns about complications from further dosage increases. Therefore, titrating to the maximum tolerated dose in line with GDMT is advisable. The patient was in a congested and unstable state during the second episode of WHF, classified as NYHA class III, and dosage increases during this period were discouraged according to both Japanese and Western guidelines.

Additionally, during the coronavirus disease 2019 pandemic, when hospital bed availability was limited and outpatient treatment was necessary, increasing BB dosage in an outpatient setting posed a risk of further HF deterioration. Therefore, ivabradine, which lowers heart rate without decreasing LV dp/dt, was selected. Ivabradine has a CRR effect and can control the increased heart rate resulting from sympathetic excitation in HF, without depressing cardiac function [19, 20]. Benstoem et al. in their recent meta-analysis reported no difference in cardiovascular mortality and severe adverse events between long-term treatment with ivabradine and placebo/usual care/no treatment in participants with HFrEF [21]. Additionally, Bryan et al. reported that ivabradine improved LVEF with CRR, reduced rehospitalizations due to WHF, further lowered the heart rate, and improved exercise capacity; however, it did not improve quality of life. No reduction in cardiovascular mortality or increase in severe adverse events was observed [22]. Therefore, further investigation is required to understand the lack of improvement in cardiovascular mortality despite inducing CRR. In the VICTORIA trial, the incidence of CRR did not differ between the groups [23]. However, several reports recently demonstrated CRR by vericiguat [24]. In our case, CRR development was attributed to the additive effect of the sixth drug, the complementary vericiguat.

The PARADIGM-HF trial and its substudy revealed that sacubitril/valsartan significantly reduced cardiovascular mortality and HFrEF hospitalization compared to angiotensin-converting enzyme inhibitors (ACEi). Furthermore, the event rate was significantly lower in the dose-maintenance group than in the dose-reduction group for both agents [25]. A retrospective study of symptomatic ATC-induced CTRCD replaced ACEi/ARB with sacubitril/valsartan and observed greater CRR, improved NYHA class, and decreased NT-proBNP. Additionally, sacubitril/valsartan demonstrated greater CRR in the low- and medium/high-dose groups [26]. Therefore, sacubitril/valsartan is the first-line RASi drug for ATC-induced CTRCD and should be increased to maximally tolerated doses.

The patient's post-chemotherapy cardiovascular monitoring was inadequate according to the current GDMT [27], including ECG and CXR performance. 2DE monitoring was performed post-acute HF admission. Interestingly, the AVPG increased with increasing CRR. The progression of LV strain on ECG over approximately two years indicated severe AS progression, which may have been caused by aortic valve calcification based on CT and 2DE findings. The increase in AVPG may have been associated with improved LV function because myocardial contractility accelerates the speed of blood flow through the aortic valve orifice. The improvement

in LV function and the timely resolution of PH outweighed AS progression. This was a valuable case in which the 2DE findings captured the pathophysiology and drug effects over time.

The long-term prognosis for patients undergoing multidrug therapy remains unknown and requires continued careful follow-up. In conclusion, this report demonstrates the potential of multidrug treatment with vericiguat and ivabradine add-ons based on quadruple therapy for the successful treatment of WHF in high-risk cancer survivors with severe ACT-induced cardiomyopathy.

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blockers
AS	Aortic stenosis
ATC	Anthracycline
AVPG	Aortic valve pressure gradient
BNP	Brain natriuretic peptide
CAG	Coronary angiography
CTCRD	Cancer treatment-related cardiac dysfunction
CRR	Cardiac reverse remodeling
CXR	Chest X-ray
ECG	Electrocardiogram
GDMT	Guideline-directed medical therapy
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
LA	Left atrial
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVMW	Left ventricular wall motion
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PH	Pulmonary hypertension
RASi	Renin-angiotensin system inhibitors
RHC	Right heart catheterization
TRmaxPG	Tricuspid regurgitant maximum pressure gradient
2DE	Two-dimensional echocardiogram
WHF	Worsening heart failure

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Authors' contributions

HO wrote the manuscript. YH, NO, KO, and HO were attending physicians of inpatient or outpatient care. KT evaluated the data from the echocardiogram and the computed tomography. AK, YH, and KT collected the data by performing the cardiac catheterization. KT supervised the presentation of the clinical case. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The Specialized Subcommittee of Niigata City General Hospital Ethics Committee approved this report.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Cardiology, Niigata City General Hospital, 463-7, Shumoku, Chuo-ku, Niigata 950-1197, Japan.

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References

- Mayer DK, Nasso SF, Earp JA. Defining cancer survivors, their needs, and perspectives on survivorship health care in the US. *Lancet Oncol*. 2017;18:e11–8.
- Chen Y, Chow EJ, Oeffinger KC, Border WL, Leisenring WM, Meacham LR, et al. Traditional cardiovascular risk factors and individual prediction of cardiovascular events in childhood cancer survivors. *J Natl Cancer Inst*. 2020;112:256–65.
- Chao C, Xu L, Bhatia S, Cooper R, Brar S, Wong FL, et al. Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: the Kaiser permanente AYA cancer survivors study. *J Clin Oncol*. 2016;34:1626–33.
- Lipshultz SE, Lipsitz SR, Mone SM, Goorin AM, Sallan SE, Sanders SP, et al. Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med*. 1995;332:1738–43.
- Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*. 2015;131:1981–8.
- Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol*. 2022;79:1757–80.
- Tromp J, Ouwerkerk W, van Veldhuisen DJ, Hillege HL, Richards AM, van der Meer P, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail*. 2022;10:73–84.
- Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med*. 2000;342:1077–84.
- Cappetta D, Rossi F, Piegari E, Quaini F, Berrino L, Urbanek K, et al. Doxorubicin targets multiple players: a new view of an old problem. *Pharmacol Res*. 2018;127:4–14.
- Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. *Front Cardiovasc Med*. 2020. <https://doi.org/10.3389/fcvm.2020.00026>.
- Banerjee P, Kotla S, Reddy Velatooru LR, Abe RJ, Davis EA, Cooke JP, et al. Senescence-associated secretory phenotype as a hinge between cardiovascular diseases and cancer. *Front Cardiovasc Med*. 2021. <https://doi.org/10.3389/fcvm.2021.763930>.
- Suter TM, Ewer MS. Cancer drugs and the heart: importance and management. *Eur Heart J*. 2013;34:1102–11.
- Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883–93.
- Castro LRV, Schittl J, Fischmeister R. Circ Res Feedback control through cGMP-dependent protein kinase contributes to differential regulation and compartmentation of cGMP in rat cardiac myocytes. *Circ Res*. 2010;107:1232–40.
- Vandenwijngaert S, Swinnen M, Walravens A-S, Beerens M, Gillijns H, Caluwé E, et al. Decreased soluble guanylate cyclase contributes to cardiac dysfunction induced by chronic doxorubicin treatment in mice. *Antioxid Redox Signal*. 2017;26:153–64.

16. Greene SJ, Bauersachs J, Brugs JJ, Ezekowitz JA, Filippatos G, Gustafsson F, et al. Management of worsening heart failure with reduced ejection fraction: JACC focus seminar 3/3. *J Am Coll Cardiol*. 2023;82:559–71.
17. Patel AN, Southern WN. BNP-response to acute heart failure treatment identifies high-risk population. *Heart Lung Circ*. 2020;29:354–60.
18. Tsutsui H, Albert NM, Coats AJS, Anker SD, Bayes-Genis A, Butler J, et al. Natriuretic peptides: role in the diagnosis and management of heart failure: a scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. *J Cardiac Fail*. 2023;29:787–804.
19. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010;376:886–94.
20. Tardif JC, O'Meara E, Komajda M, Böhm M, Borer JS, Ford I, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodeling and function: results from the SHIFT echocardiography substudy. *Eur Heart J*. 2011;32:2507–15.
21. Benstoem C, Kalvelage C, Breuer T, Heussen N, Marx G, Stoppe C, et al. Ivabradine as adjuvant treatment for chronic heart failure. *Cochrane Database Syst Rev*. 2020;11:CD013004.
22. Bryan RS, Huang B, Liu G, Yang Y, Luo S. Impact of ivabradine on the cardiac function of chronic heart failure reduced ejection fraction: meta-analysis of randomized controlled trials. *Clin Cardiol*. 2021;44:463–71.
23. Pieske B, Pieske-Kraigher E, Lam CSP, Melenovsky V, Sliwa K, Lopatin Y, et al. Effect of vericiguat on left ventricular structure and function in patients with heart failure with reduced ejection fraction: the VICTORIA echocardiographic substudy. *Eur J Heart Fail*. 2023;25:1012–21.
24. Imamura T, Kinugawa K. Initial experience of vericiguat add-on therapy upon fantastic four medical therapy in a patient with systolic heart failure. *J Cardiol Cases*. 2022;26:429–31.
25. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, et al. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *Eur J Heart Fail*. 2016;18:1228–34.
26. Martín-García A, López-Fernández T, Mitroi C, Chaparro-Muñoz M, Moliner P, Martín-García AC, et al. Effectiveness of sacubitril-valsartan in cancer patients with heart failure. *ESC Heart Fail*. 2020;7:763–7.
27. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43:4229–361.

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