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Review of the Response to Heart Failure Treatment with Bisoprolol in Hematological Patients with Post-Chemotherapy Cardiotoxicity, Evaluated by B-Type Natriuretic Peptide Levels, A Case Series

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Abstract **Case Report**

Anthracycline-induced cardiotoxicity is a significant and dose-dependent complication in cancer patients, associated with heart failure and high morbidity and mortality. Its pathophysiology includes oxidative stress, mitochondrial damage, apoptosis, and alterations in iron metabolism, which impair myocardial contractility. It can manifest acutely, early, or late, with the latter being the most frequent. Early diagnosis relies on biomarkers such as BNP and troponins, along with imaging studies. Prevention includes limiting the cumulative dose and using dexrazoxane. Treatment with ACE inhibitors and bisoprolol improves cardiac function and clinical prognosis. In this article, we review the response to bisoprolol treatment for heart failure in six hematological patients with post-chemotherapy cardiotoxicity, who underwent follow-up transthoracic echocardiograms and had their response assessed by B-type natriuretic peptide levels for at least four weeks.

Keywords: Cardiotoxicity, anthracyclines, heart failure, echocardiogram, bisoprolol.

INTRODUCTION

Cancer treatment carries medium- and long-term complications, the main one being premature cardiovascular disease, due to exposure to chemotherapy drugs such as anthracyclines. Therefore, cardiovascular disease is the leading cause of death in cancer survivors [1].

The mechanism of cardiotoxicity caused by tetracyclic antidepressants is the release of free radicals and peroxides that damage cardiac fibers, inhibit protein synthesis, and induce the apoptosis cascade and cell death. Anthracyclines inhibit DNA and RNA synthesis, causing strand breakage with mutagenic and carcinogenic effects, formation and deposition of ferric iron in cardiomyocytes, decreasing the quinone group, forming superoxide radicals and hydrogen peroxide, which damage the integrity of the mitochondrial membrane, inhibit the entry of intracellular calcium and sodium ions, necrosis and apoptosis, decreasing myocardial contractility, and causing cardiac fibrosis, heart failure, and dilated and/or restrictive cardiomyopathy [1].

To reduce cardiotoxicity that causes subclinical damage, we have three options: a) decrease the concentration of anthracyclines (no greater than 300 mg/m2 cumulative); b) develop less cardiotoxic analogues (liposomal anthracyclines, daunorubicin); and c) administer cardioprotective agents to prevent myocardial remodeling and progression to heart failure, such as dexrazoxane (an iron chelator and oxygen free radical scavenger). For treatment, we have diuretics, angiotensin-converting enzyme inhibitors such as enalapril, and beta-blockers such as carvedilol, statins, metoprolol and bisoprolol, vitamins A, E, and C,

coenzyme Q10, and carnitine. These options can recover more than 50% of the LVEF, resulting in an 85% survival rate and increased heart rate [1].

Cardiotoxicity (CTX) is the leading non-cancerous cause of serious complications and the risk persists for up to 45 years after the end of treatment; it is also the second leading cause of death, after secondary cancer [2].

Since the 1980s, anthracyclines, including doxorubicin, daunorubicin, epirubicin, and idarubicin, have been fundamental to the treatment of various hematologic and solid malignancies, such as Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), acute leukemias, breast cancer (BC), ovarian cancer, and sarcomas. In clinical practice, the use of anthracyclines is limited by dose-dependent cardiotoxicity, which leads to systolic and diastolic cardiac dysfunction and, in less common cases, overt heart failure (HF) [3].

Anthracycline-related cardiotoxicity can be classified according to its temporal relationship to drug administration. Acute cardiotoxicity can develop at any time during or shortly after anthracycline treatment and is usually reversible upon discontinuation of the drug; it is uncommon, occurring in <1% of cases. Early-onset cardiotoxicity can appear during the first year after treatment, often associated with an asymptomatic decrease in left ventricular ejection fraction (LVEF); this form accounts for 98% of all cardiotoxicity cases in a large cohort of anthracycline-treated patients. Late-onset cardiotoxicity, which becomes clinically apparent more than one year after exposure, usually presents as hypokinetic or dilated cardiomyopathy with obvious symptoms of heart failure [3].

Similarly, intensive dose approaches have demonstrated improved survival in adults with acute lymphoblastic leukemia (ALL) in whom induction regimens include anthracyclines along with vincristine and corticosteroids. Initially, no significant cardiovascular toxicity was observed, but a higher cumulative dose of anthracyclines can lead to delayed cardiotoxicity, which is of particular concern in a young population with a potentially curable disease. Hodgkin lymphoma (HL) and most non-pathological HLs with aggressive behavior are dependent on treatment regimens containing anthracyclines [3].

Regarding alterations in cell death pathways, anthracyclines are known to induce myocyte apoptosis via both intrinsic and extrinsic pathways. Recent studies have also highlighted how pyroptosis and ferroptosis contribute to the loss of viable myocytes, primarily through the overexpression of non-coding RNA induced by terminal differentiation, leading to iron dysregulation and lipid peroxidation, respectively [3].

Anthracyclines are not completely cleared from cardiomyocytes, leading to cardiac deposition that increases with each infusion and begins to induce cardiotoxicity. Morphological and functional damage eventually occurs when the cumulative dose causes the size of these cardiac anthracycline deposits to exceed the cardiomyocytes' detoxification capacity. With doxorubicin, the threshold between low and high risk of heart failure due to anthracycline accumulation is defined as between 250 and 300 mg/m². Conversely, cardioprotective strategies can cause cardiotoxicity to occur at higher cumulative doses [3].

Neuroproteins (NPs), including B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are essential cardiac hormones for the diagnosis and treatment of heart failure (HF). NPs have been extensively investigated in predicting cardiac retinopathy of prematurity (C-TR), but interpretation of the results must consider confounding factors such as renal function, body weight, use of angiotensin receptor neprilysin inhibitors, and cardiac arrhythmias. Although several studies have demonstrated increases in B-type natriuretic peptide in patients treated with anthracyclines and a persistent elevation of NT-proBNP after chemotherapy, the correlations between these laboratory findings and the prediction of cardiotoxicity endpoints in multiple studies have been variable. Furthermore, the Cardiac Cancer Toxicity Registry did not find baseline NT-proBNP to be a strong predictor of the degree of cardiac dysfunction detected after chemotherapy. Consequently, although NP elevations are often observed at baseline and during chemotherapy in patients who may eventually develop CDRTC, the predictive value of such elevations in studies remains controversial [3].

The multifactorial nature of anthracycline cardiotoxicity suggests that circulating markers of oxidative stress (e.g., myeloperoxidase), inflammation (e.g., C-reactive protein and interleukin-6), and fibrosis (e.g., soluble tumorigenicity suppressor 2 and galectin-3) could be useful for predicting cardiotoxicity. A patient's genomic, transcriptomic, proteomic, and metabolomic profile could explain the diverse cardiovascular vulnerabilities observed in patients. Furthermore, novel biomarkers must be tailored to specific cancer types to avoid false positives caused by the cancer itself. While the development of biomarkers that can unequivocally diagnose CTRCD-induced cardiotoxicity is appealing, it is crucial to consider how the mechanisms of cardiotoxicity overlap with cancer biology and comorbidities [3].

Neurohormonal blockade is recommended to prevent CTRCD in patients receiving high-dose anthracyclines (≥250 mg/m²) or with pre-existing cardiovascular disease. Statins may be beneficial for lymphoma patients receiving high-dose anthracyclines [3].

The use of biomarkers such as troponin and NT-proBNP, in combination with imaging techniques such as echocardiography and cardiac magnetic resonance imaging, allows for the detection of subclinical changes in ventricular function. Furthermore, ejection fraction and global longitudinal strain (GLS) are key parameters for the early identification of ventricular dysfunction [3].

Anthracycline-induced cardiotoxicity (AIC) is classified as acute or chronic based on the time of onset, and chronic cardiotoxicity can occur within one year or several years after completion of anthracycline treatment. Both early and long-term cardiotoxicity contribute to a poor prognosis in cancer patients [4].

Anthracyclines disrupt intracellular iron homeostasis induced by heme oxygenase 1 (HO1) and glutathione peroxidase 4 (GPX4), resulting in increased free iron in cardiomyocytes, lipid peroxidation in cell membranes and mitochondria, leading to iron-induced cell death and myocardial injury. This process persists during treatment. Several strategies have been proposed to mitigate anthracycline-induced ferroptosis. Iron chelators such as dexrazoxane, deferoxamine, and ciclopirox, along with iron-restricted diets, are recommended to attenuate iron accumulation, protect mitochondrial structure and function, and reduce the incidence of cardiotoxicity [4].

Anthracyclines can affect the dynamic equilibrium of mitochondrial fusion and increase the expression of dynamin-related mitochondrial fission protein 1 (Drp1), inhibit the expression of mitochondrial fusion proteins such as mitofusin 2 (MFN2) and optic atrophy 1 (OPA1), induce dysregulation of mitochondrial autophagy, and contribute to mitochondrial fragmentation and dysfunction, which can cause cardiotoxicity. Anthracyclines can also interfere with mitochondrial substrate metabolism, particularly fatty acid metabolism and the electron transport chain, which can result in the blockage of adenosine triphosphate (ATP) synthesis and induce the opening of the mitochondrial permeability transition pore (mPTP), ultimately leading to cell apoptosis [4].

Among the emerging mechanisms of AIC, multiple novel biomarkers have been shown to have a significant impact on disease progression and treatment response. Research shows that markers of inflammation, fibrosis, and oxidative stress—C-reactive protein (CRP), myeloperoxidase (MPO), growth differentiation factor 15 (GDF-15), and glycogen phosphorylase BB (GPBB), an enzyme essential for glucose metabolism—were elevated after anthracycline treatment and were associated with a reduced risk of LVEF [4].

Both acute and chronic cardiotoxicity caused by anthracyclines are dose-dependent. For example, studies have shown that when the cumulative dose of doxorubicin (DOX) exceeded 600 mg/m², the incidence of cardiotoxicity increased to 36%, and when the cumulative dose exceeded 550 mg/m², the incidence of heart failure reached 26%. The cumulative lifetime dose of DOX is generally limited to 450 mg/m² [4].

To reduce cardiotoxicity without compromising the anticancer effect, researchers also developed an iron chelator, dexrazoxane, as a cardioprotective agent against anthracycline cardiotoxicity [4].

Results from previous clinical trials showed that while early treatment with beta-blockers and ACE inhibitors/ARBs in patients with breast cancer or non-Hodgkin lymphoma was associated with a reduction in left ventricular end-diastolic diameter (LVEDD) and retained global longitudinal strain (GLS), it did not alter the decline in left ventricular ejection fraction (LVEF), an important indicator for identifying and monitoring cardiotoxicity. More importantly, significant differences in cardiac troponin (cTn) concentrations were observed without changes in LVEF before and after treatment with these cardioprotective agents [4].

Studies have shown that metformin can inhibit the release of cytochrome C from mitochondria, reduce ROS production, and activate the adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) pathway to inhibit mitochondrial oxidative stress damage caused by anthracyclines. Studies have shown that sodium-glucose cotransporter-2 (SGLT-2) inhibitors, also used as hypoglycemic agents, can improve cardiac mitochondrial dysfunction caused by anthracyclines and increase intracellular ATP levels. Furthermore, SGLT-2 inhibition has been reported to be associated with a lower risk of cardiac events in patients treated with anthracyclines. Significantly, more large-scale, high-level, evidence-based clinical trials are needed to corroborate the beneficial effects of these emerging cardioprotective agents [4].

The 2022 ESC Cardiovascular Oncology Guidelines recommend that, in addition to cardiac imaging for patients undergoing anthracycline-based chemotherapy, continuous monitoring, such as cardiac serum troponin and natriuretic peptide, is needed for risk stratification and to promote early diagnosis and treatment. However, experts have raised concerns about the potential limitations of these traditional biomarkers, including troponin and natriuretic peptide, as nonspecific markers susceptible to influences such as gender, race, weight, and other patient comorbidities. To overcome the limitations of traditional biomarkers, researchers are exploring more specific and sensitive biomarkers. In addition to the novel circulating biomarkers mentioned above, galactin-3, associated with myocardial fibrosis, has shown good predictive value in animal models, but a clear association with reduced LVEF has not been observed in clinical studies. This could be related to the inability of echocardiography to accurately assess myocardial fibrosis. The combination of traditional

biomarkers (such as cTnT, NT-proBNP) with novel biomarkers (such as mRNA, MPO) can significantly improve the sensitivity and specificity of early diagnosis and prognosis assessment of ICA [4].

Risk factors for anthracycline-induced cardiotoxicity include genetic factors, cumulative dose, female sex, and renal failure. Risk factors shared with trastuzumab include age <15 and >65 years, hypertension, diabetes, ischemic heart disease, low-normal ejection fraction (50-55%) prior to treatment, history of heart failure or cardiac dysfunction related to chemotherapy, combination of chemotherapy and thoracic radiotherapy; obesity (LVEM >30 kg/m²) and sedentary lifestyle are more strongly associated with trastuzumab-induced cardiotoxicity

Based on the degree of risk for cardiotoxicity, antineoplastic drugs are classified as follows:

- High risk: anthracyclines, cyclophosphamide and trastuzumab.
- Moderate risk: docetaxel, pertuzumab, sunitinib, sorafenib.
- Low risk: bevacizumab, dasatinib, imatinib, and lapatinib

Cardiotoxicity can present in different forms:

type 1, through an anthracycline-like effect or "anthracycline effect," which can be acute, dose-independent, transient, and due to type 1 hypersensitivity; or the chronic, dose-dependent, cumulative, and irreversible form. Type 2 cardiotoxicity is similar to that of trastuzumab or "trastuzumab effect," with reversible injury because it does not cause ultrastructural damage to cardiomyocytes (5).

In patients scheduled to receive anthracycline chemotherapy, it is also relevant to know the cumulative dose of total anthracycline that is planned, so that a dose ≥250 mg/m2 of doxorubicin or equivalent should be considered as high risk (6)

Four recent position papers resulting from the collaboration between the ESC HFA Cardio-Oncology Study Group, the ESC-CCO, and ICOS suggest that measuring cardiac serum biomarkers (cardiac troponin [cTn] I or T and natriuretic peptides [NPs], such as brain natriuretic peptide [BNP] or the N-terminal fragment of brain natriuretic propeptide [NT-proBNP]) can aid in the initial cardiovascular risk stratification of patients scheduled for cancer treatments, including anthracyclines, human epidermal growth factor receptor 2 (HER2)-targeted therapies, vascular endothelial growth factor inhibitors (VEGF), proteasome inhibitors (PIs), immune checkpoint inhibitors (ICIs), and chimeric antigen receptor (CAR-T) and tumor-infiltrating lymphocyte (TIL)-based therapies, allowing the identification of those who They may benefit from cardioprotective treatment [6].

Bile phosphate progesterone (BNP) is another potential biomarker for cardiovascular (CV) risk stratification. Several studies have described the role of baseline BNP levels or changes in BNP in predicting future cardiovascular events. In patients with multiple myeloma (MM), pre-treatment BNP levels may be predictive markers of subsequent adverse cardiovascular events. In a study of 109 patients with relapsed MM, BNP levels >100 pg/mL or NT-proBNP levels >125 pg/mL before initiating carfilzomib treatment were associated with an odds ratio of 10.8 for subsequent adverse cardiovascular events. ⁶⁶ Therefore, baseline BNP levels are recommended in high- and very-high-risk patients and should be considered in moderate- and low-risk patients before protease inhibitor (PI) therapy. ⁶

DEFINITIONS OF CARDIOVASCULAR TOXICITY RELATED TO CANCER TREATMENT:

DC-RTC (cardiac dysfunction related to cancer treatment)

Symptomatic DC-RTC (IC):

- Very serious: Heart failure requiring inotropic support, mechanical circulatory assistance, or consideration of transplantation
- Severe: Hospitalization for heart failure
- Moderate: Need for outpatient diuretic intensification and treatment for heart failure
- Mild: Mild heart failure symptoms, treatment intensification is not required

Asymptomatic DC-RTC:

- Severe: Further reduction in LVEF to <40%
- Moderate: Further reduction in LVEF of ≥10 percentage points to LVEF of 40–49%
  OR a further reduction in LVEF of <10 percentage points to LVEF of 40–49% AND a further relative decrease in SGL of >15% compared to baseline
  or new increase in cardiac biomarkers
- Mild: LVEF ≥ 50% AND new relative decrease in SGL of >15% compared to baseline
  And/or a new increase in cardiac biomarkers

Anthracycline equivalence doses	Doxorubicin	Epirubicin	Daunorubicin	Mitoxantrone	Idarubicin
CV toxicity dose relationship	1	0.8	0.6	10.5	5
Isoequivalent dose	100 mg/m2	125 mg/m2	167 mg/m2	9.5 mg/m2	20 mg/m2

Other novel biomarkers for stratifying the risk of TCV-RTC before cancer treatment have also attracted interest; however, published data are scarce. These include myeloperoxidase, C-reactive protein, galectin-3,

arginine-nitric oxide metabolites, growth differentiation factor-15, placental growth factor, FMS-like tyrosine kinase-1, microribonucleic acids, and immunoglobulin E. Currently, there is no evidence to support the routine measurement of these new biomarkers, and further research is needed to establish their potential utility [6].

Anthracycline-induced cardiotoxicity (AIC) is a dose-limiting and potentially fatal complication of anthracycline administration that can occur during any period of chemotherapy. The main representative features are arrhythmias, pericardial effusion, and myocardial ischemia. AIC can contribute to heart failure and decrease survival. The mechanisms of AIC are complex and include free radicals, calcium overload, altered energy metabolism, and apoptosis [7].

Cardiotoxic effects become more pronounced as the cumulative dose increases. The risk of congestive heart failure is positively correlated with anthracycline doses. Early monitoring and timely intervention are essential to prevent progression to irreversible cardiac damage. Beta-blockers can treat heart failure by stimulating the Gs-AC-cAMP-PKA signaling pathway to produce positive inotropic effects in cardiac myocytes [7].

The NMA results showed that carvedilol was superior to bisoprolol and nebivolol in delaying the decline in LVEF. The likelihood classification results indicated that carvedilol was the best beta-blocker for preventing HFrEF. Furthermore, bisoprolol and nebivolol were equally advantageous in mitigating the decline in LVEF [7].

A network meta-analysis of clinical trials on outcomes in HFrEF included the CIBIS trials with bisoprolol and the SENIORS trial with nebivolol. No significant differences were observed between bisoprolol and nebivolol in terms of effects on all-cause mortality, cardiovascular mortality, or sudden death [8].

Three neurohormonal systems are fundamental to the progression of heart failure (HF): the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and the natriuretic peptide system (NPS). These systems initially help maintain adequate cardiac output by increasing heart rate (HR) and blood volume. However, chronic activation leads to adverse cardiac remodeling and progression to HF. According to the CSI-KHFR, the 5-year mortality rate in patients with HF is reported to be 59%, with sudden cardiac death accounting for 46% of cases, demonstrating a poor prognosis associated with this condition [9].

Bisoprolol, a cardioselective beta-blocker (BB), plays a well-established role in the treatment of heart failure with reduced ejection fraction (HFrEF) and stable angina, primarily by reducing sympathetic hyperactivity and myocardial oxygen demand through inhibition of sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) hyperactivity. These characteristics also make bisoprolol a rational choice for the long-term treatment of cardiovascular disease (CVD), particularly in the Indian context, where comorbidities such as chronic kidney disease (CKD), diabetes, and chronic obstructive pulmonary disease (COPD) are common [9].

CLINICAL CASES

The following is a series of 6 cases in which heart failure was documented in people who were receiving chemotherapy, presenting elevated serum levels of BNP and loss of functional class, starting treatment with bisoprolol for at least 4 weeks presenting a decrease in BNP levels, improvement of functional class and a decrease in dyspnea.

Case 1.

A 64-year-old female patient presented with a T-cell and histiocyte-rich large B-cell non-Hodgkin lymphoma with a cell proliferation index of 60%. She received 5 cycles of CHOP-R chemotherapy and 6 cycles of NICE chemotherapy, experiencing loss of functional class, dyspnea on minimal exertion, and oxygen dependence during hospitalization. As part of the management, a transthoracic echocardiogram was performed (Table 1) and serum BNP levels were measured. Subsequent studies revealed heart failure with preserved ejection fraction, so oral treatment with bisoprolol was initiated at a dose of 5 mg every 24 hours. After 1 month of treatment, BNP levels decreased to 18% of the initial serum value (Table 2), with clinical improvement and a reduction in symptoms.

Table 1: Transthoracic echocardiogram 05/08/2025

Variable	Worth
FEVI	55%
TAPSE	15 mm
PSAP	30 mm Hg
Contractility	Preserved
Valvular heart disease	Trivalved aortic valve, with mild sclerosis, without lesions.
Pericardium	Minimal pericardial effusion, without hemodynamic compromise.

Table 2: Serum BNP values

Date	pg/ml value
04.11.25	310
14.12.25	56

Case 2

A 22-year-old male patient presented with acute lymphoblastic leukemia of common B-cell precursors (L2) of the FAB cell line, with immunohistochemistry showing CD34+, CD10+, TdT+, PAX5+, and CD20+, and a history of pulmonary artery stenosis since birth. He received chemotherapy with a modified LALIN regimen, as well as one cycle of methotrexate with folinic acid rescue. During hospitalization, as part of the management, a transthoracic echocardiogram was performed (Table 3), revealing pulmonary artery stenosis as an anatomical variant. Serum BNP levels were also measured, leading to a diagnosis of heart failure with preserved ejection fraction. However, due to the congenital heart disease, oral bisoprolol treatment was reserved. He continued cardiology follow-up, and after two months, elevated BNP levels were observed (Table 4). Due to cardiotoxicity and increased symptoms of heart failure, oral treatment with bisoprolol was initiated at a dose of 1.25 mg every 24 hours. After 3 months of treatment (Table 4), BNP levels decreased to 7.32% compared to the serum value at the onset of cardiotoxicity, with clinical improvement and a decrease in overload.

Table 3: Transthoracic echocardiogram 10/30/2025

Variable	Worth
FEVI	64%
TAPSE	24 mm
PSAP	34 mm Hg
Contractility	Preserved
Valvular heart disease	Pulmonary valve thickening
Pericardium	Normal.

Table 4: Serum BNP values

Date	pg/ml value
31.10.25	55
10.11.25	75
21.11.25	4,218
18.02.26	309

Case 3

A 39-year-old male diagnosed with high-risk B-cell acute lymphoblastic leukemia L2 (ALL) received chemotherapy based on the LALIN regimen with 3 doses of vincristine and 1 dose of methotrexate. During hospitalization, he experienced a decline in functional class and progressive dyspnea on moderate and mild exertion. As part of the protocol, a transthoracic echocardiogram (Table 5) and serum BNP levels were measured, revealing heart failure with preserved ejection fraction (HFpEF). Oral bisoprolol treatment was initiated at a dose of 2.5 mg every 24 hours, resulting in a decrease in BNP levels to 48% of the initial serum value after 1 month of treatment (Table 6).

Table 5: Transthoracic echocardiogram 10/09/2025

Variable	Worth
FEVI	70%
TAPSE	24 mm
PSAP	30 mm Hg
Contractility	Preserved
Valvular heart disease	Structurally normal atrioventricular and semilunar valves.
Pericardium	Normal.

Table 6: Serum BNP values

Date	pg/ml value
08.12.25	680
26.01.26	331

Case 4

A 29-year-old male with a history of WHO stage I HIV since 2018 on antiretroviral therapy with Dolutegravir/Lamivudine with an HIV viral load <40 copies, CD4+189. He underwent a diagnosis of hemophagocytic lymphohistiocytosis secondary to

invasive fungal infection in September 2025, with a bone biopsy on 10/16/25 with a tissue report (image 1) for age and sex with the presence of fungal hyphae (GMS positive), with local fungal infection, Grocott and PAS positive focal in hyphae, Ziehl-Neelsen negative; receiving treatment with amphotericin B at a cumulative dose of 450 mgs and chemotherapy with protocol HLL 94 which is administered every 7 days for 10 weeks. During hospitalization, the patient experienced dyspnea on moderate exertion, loss of functional class with inability to ambulate, so as part of the protocol, serum BNP levels were measured and, given the elevated values, a diagnosis of heart failure was established and oral treatment with bisoprolol was started at a dose of 5 mg every 24 hours with a decrease in BNP levels to 11% of the total initial serum value after 2 months of treatment (table 7), improvement in gait, disappearance of dyspnea and continued in follow-up by hematology and infectious diseases.

Image 1. Bone biopsy

Immunohistochemistry		
Staining	**Result**	**Comment**
PAS	Positive	Presence of yeast
GROCOTT	Positive	Presence of yeast
Z. N	Negative	There are no mycobacteria

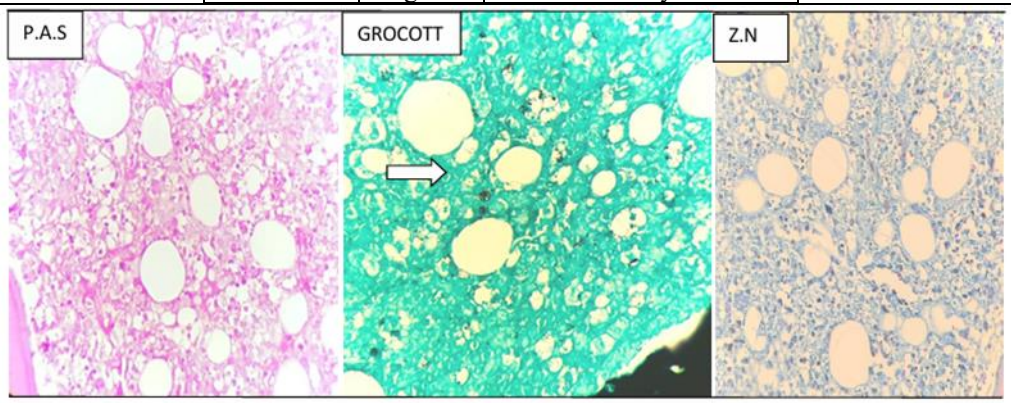

Table 7: Serum BNP values

Date	pg/ml value
25.09.25	759
18.11.25	84

Case 5.

A 79-year-old female patient diagnosed with grade 1 follicular non-Hodgkin lymphoma, B-cell immunophenotype, CD20 positive, with a proliferation index of 20%, received CHOP-R chemotherapy. As part of the protocol and due to loss of functional class, a transthoracic echocardiogram was performed (Table 8) and serum BNP levels were measured, revealing heart failure with preserved ejection fraction. Oral bisoprolol treatment was initiated at a dose of 5 mg every 24 hours. During hospitalization, studies showed a decrease in BNP levels to 85% of the initial serum value after 6 weeks of treatment (Table 9), with a reduction in symptoms.

Table 8: Transthoracic echocardiogram 01/14/2026

Variable	Worth
FEVI	61%
TAPSE	27 mm
PSAP	30 mm Hg
Contractility	Preserved
Valvular heart disease	Trivalved aortic valve, with sclerosis and slight calcification of its leaflets. Mitral valve with sclerosis of its leaflets and calcification of the annulus.
Pericardium	No alterations.

Table 9: Serum BNP values

Date	pg/ml value
14.01.26	521
29.02.26	443

Case 6.

A 35-year-old male patient diagnosed with Acute Lymphoblastic Leukemia L2, who received chemotherapy treatment based on HCVAD and the LALIN regimen. Clinically, he presented with tachycardia and dyspnea on moderate exertion. As part of the protocol, a transthoracic echocardiogram was performed (Table 10) and serum BNP levels were measured, revealing heart failure with preserved ejection fraction. Oral treatment with bisoprolol at a dose of 2.5 mg every 24 hours was initiated as an antifibrotic agent. During hospitalization, studies showed a decrease in BNP levels to 85% of the initial serum value after 8 months of treatment (Table 11), with a reduction in symptoms.

Table 10: Transthoracic echocardiogram 08/22/2025

Variable	Worth
FEVI	58%
TAPSE	27 mm
PSAP	30.7 mm Hg
Contractility	Preserved
Valvular heart disease	Tricuspid valve with mild functional insufficiency, speed 2.3 meters/second and maximum gradient of 25.7 mm Hg.
Pericardium	No alterations.

Table 11: Serum BNP values

Date	pg/ml value
21.08.25	177
17.04.26	37

RESULTS AND DISCUSSION

Administering beta-blockers to patients with heart failure improved left ventricular function. Beta-blockers not only block the cardiac remodeling process but can also repair it. The Bisoprolol Heart Failure Study (CIBIS)-I showed that bisoprolol use can reduce hospitalization rates, the incidence of pulmonary edema, ventricular tachycardia (VT), and ventricular fibrillation (VF) in patients with heart failure. The larger CIBIS-II study demonstrated that bisoprolol use can reduce mortality, sudden cardiac death, and hospitalization rates in patients with heart failure [10].

Bisoprolol is an evidence-based BB recommended in guidelines for the management of HFrEF and has demonstrated significant efficacy and safety in patients with HFrEF through several randomized controlled trials (CIBIS, CIBIS II and CIBIS III) [9].

A meta-analysis of the CIBIS I and CIBIS II trials also demonstrated the effectiveness of bisoprolol in reducing overall mortality, cardiovascular mortality, and hospitalizations [9].

Cardinale (2015) studied 2,625 patients with various types of cancer who received anthracycline-based chemotherapy and were followed for a median of 5.2 years. Ninety-eight percent of cardiotoxicity (symptomatic reduction in LVEF) was found to occur within the first 12 months after anthracycline therapy. This study followed patients until after the sixth chemotherapy session, or approximately 5 months after initiating anthracycline chemotherapy. Undocumented cardiotoxicity events may still have occurred, given the shorter follow-up period of less than 12 months. To obtain accurate data on the number and type of cardiotoxicity in patients receiving anthracycline chemotherapy, follow-up of at least 12 months after the start of the first chemotherapy cycle is required [10].

In a systematic review and meta-analysis of 16 studies that recruited more than 27,000 patients with HFpEF (i.e., LVEF ≥50%), the pooled analysis of the included cohort studies, with varying follow-up durations, showed a 19% reduction in the risk of all-cause mortality. Sensitivity analyses confirmed the mortality benefit. Compared with younger patients (<75 years), older patients showed a significant 21% reduction in mortality. Rehospitalization for heart failure or its combined factor with all-cause mortality was similar between the beta-blocker and control groups. Beta-blockers may potentially improve ventricular diastolic function and remodeling, partly due to their effect on improving endothelial function by exerting antioxidant and anti-inflammatory effects [11].

Although beta-blockers are considered the cornerstone of treatment for heart failure with reduced ejection fraction, their benefit in HFpEF remains uncertain, and there is currently no consensus on their efficacy in this group [11].

CONCLUSIONS

Chemotherapy-associated cardiotoxicity, particularly that caused by anthracyclines, represents a significant complication that impacts the prognosis and quality of life of cancer patients. In this case series, the presence of heart failure with preserved ejection fraction, accompanied by elevated BNP and functional decline,

highlights the importance of close monitoring during treatment. The use of bisoprolol showed consistent benefits, reflected in the reduction of biomarkers, symptomatic improvement, and recovery of functional class. These findings support the role of beta-blockers as a therapeutic strategy in subclinical cardiotoxicity. However, evidence regarding heart failure with preserved ejection fraction remains limited and requires further research, as well as larger studies to establish definitive recommendations. Early detection and timely management remain essential.

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