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Article

The role of brain natriuretic peptide biomarker in the detection of cardiotoxicity

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ABSTRACT

Background: In the domain of cardio-oncology, it is widely acknowledged that chemotherapy, notwithstanding its potential curative effects, can inflict severe harm upon bystander tissues. This damage can give rise to a variety of cardiovascular toxicities that are life-threatening, as well as induce various side effects such as myocardial infarction and heart failure. Over time, cardiotoxicity causes substantial morbidity and mortality among oncology patients, particularly as a result of dysfunction in the left ventricle. There is a growing focus on the utilization of biomarkers for early detection of cardiotoxicity, prior to its irreversible progression. Studying natriuretic peptides, especially brain natriuretic peptides (BNP) and their inactive fragment N-terminal pro-brain natriuretic peptide **(**NT-proBNP) , has become a meaningful way to find and predict cardiotoxicity, especially in cancer treatment. They were released in response to ventricular strain, offering significant insights into cardiac function beyond the capabilities of echocardiography.

Aim: This literature review aims to look at BNP as a biomarker to monitor and detect cardiotoxic effects in patients who are getting treatments that are known to affect heart function. The incidence and characteristics of the cardiotoxic effects of antineoplastic drugs are also examined, emphasizing the pathophysiological mechanisms. In addition, it shows how important it is to quickly find and fix cardiovascular risk factors and how important it is to keep a close eye on the heart during anticancer treatment to avoid heart damage.

results

Cardiac biomarkers, particularly BNPs are the most promising clinical tool for assessing baseline risk and detecting early cardiac injury or strain which may predict future alterations in LVEF and development of HF in different cardiotoxic drugs .

Conclusion

BNP represents a potential complement or replacement for echocardiographic monitoring of chemotherapy-related cardiac toxicity, allowing for earlier detection of the degree of cardiac damage occurring during treatment . There is a hope that the use of biomarkers can help in identifying patients undergoing treatment who are at high risk for cardiotoxicity .

Keywords: Cardiotoxicity; BNP; Brain natriuretic peptide; Cardiac biomarkers.

1. Introduction

A wide range of potential adverse cardiovascular effects may result from cancer treatment. The National Cancer Institute and the National Heart, Lung, and Blood Institute established a conceptual framework 2013 to delineate cardiotoxicity associated with cancer treatments. Cardiotoxicity includes ventricular dysfunction, heart failure (HF), arrhythmias, coronary artery disease/acute coronary syndrome (ACS), hypertension, and thromboembolic events [1].

The precise incidence of these conditions about cancer treatment remains uncertain. Two principal categories of cardiac infarction have been postulated, albeit an overly simplistic classification that fails to capture the intricate effects of multiple chemotherapeutic agents sufficiently: type 1 cardiotoxicity induced by chemotherapy (direct myocyte death) and type 2 cardiotoxicity induced by chemotherapy (reversible myocyte dysfunction). Anthracyclines, which are agents linked to type 1 cardiotoxicity, have been hypothesized to have a propensity to induce

long-term effects; consequently, there is an urgent requirement to develop more sophisticated diagnostic instruments that can assess lifetime risk. Conversely, drugs that cause type 2 cardiotoxicity, such as trastuzumab, are not associated with long-term cardiotoxicity [2] . The aim of this review is to highlight the importance of cardiac biomarkers, particularly BNP in the diagnosis, screening and monitoring of cardiotoxicity during and after cancer treatment.

1.1 Risk factors.

About risk factors for cardiotoxicity, it has been determined that age, cumulative dose of chemotherapeutic agents, and quantity of irradiation are each independently associated with an increased likelihood of developing cardiotoxicity. Diabetes and alcohol consumption have been identified as risk factors that elevate the possibility of cardiotoxicity in anthracycline-treated patients. Comorbidities including obesity and hypertension, alongside coronary artery disease and tobacco use, are linked to an elevated likelihood of left ventricular (LV) dysfunction and symptomatic HF in breast cancer patients undergoing trastuzumab monoclonal antibody therapy. Before receiving a cancer diagnosis, the presence of these pre-existing comorbidities elevates the likelihood of developing cardiovascular disease. Some articles advocate for the "multiple hit" hypothesis, which posits that lifestyle risk factors have an indirect impact on cardiovascular health. At the same time, adjuvant chemotherapy induces a direct cardiotoxic effect, thereby collectively elevating the risk of cardiovascular disease (CVD) [3].

Initially, it was determined that anthracyclines and radiation therapy induce cardiovascular complications. Pericarditis, arrhythmias, myocarditis, and cardiac dysfunction are all adverse cardiovascular consequences. Varying frequencies and severity of cardiotoxicity have been documented in relation to human epidermal growth factor receptor 2 (HER2) inhibitors (e.g., trastuzumab), vascular endothelial growth factor (VEGF) signaling inhibitors, and multi-targeted tyrosine kinase inhibitors. With the proliferation of anti-cancer therapies, there is a growing need for vigilance regarding the surveillance and detection of cardiac adverse effects, both anticipated and known [4].

Cardiotoxicity may manifest within a few years, acutely or sub acutely after oncologic therapy exposure. Clinical HF, also known as Left ventricular dysfunction, is a frequently observed and routinely assessed adverse effect associated with chemotherapies. In contemporary

approaches, routine echocardiography is frequently utilized to assess for new or progressive Left ventricular dysfunction. Early in the progression of cardiac infarction, biomarkers might offer valuable insight. Comorbidities commonly observed in patients receiving trastuzumab, such as hypertension, coronary artery disease, age, or atrial fibrillation/flutter, are incorporated into risk factor scores to estimate the three-year risk of developing HF [5].

Biomarkers have not been evaluated as components of the prediction profile in these risk scores. Prediction before therapy initiation may not be the only function of cardiotoxicity surveillance during treatment. Echocardiographic parameters, including fractional shortening, strain, and left ventricular ejection fraction (LVEF), have been employed in limited-scale investigations. The third domain that remains substantially unaddressed is the long-term monitoring of CVD development following therapy. Despite the expanding body of literature in this field, the ideal duration of cardio-toxicity surveillance for individual chemotherapeutic agents and the prospective time span between cancer therapy and the occurrence of cardio-toxicity are still not fully understood [6].

1.2 Mechanisms

The precise mechanism by which antipsychotics, anthracyclines, or drugs induce cardiotoxicity is unknown; however, it probably involves multiple contributing factors. It is imperative to comprehend the mechanisms underlying anthracycline-induced cardiotoxicity to implement effective cardioprotective measures. Several mechanisms have been suggested ,one of which involves the formation of iron complexes that can undergo reactions with oxygen (O_2) to produce superoxide anion ($^{\bullet}O_2^-$), hydrogen peroxide (H_2O_2), or enter the Haber-Weiss reaction to yield hydroxyl radical (•OH), alternatively, they can react directly with hydrogen peroxide (H2O2) to yield hydroxyl radical (•OH). The observed effects include an increase in the generation of reactive oxygen and nitrogen species, lipid peroxidation, inflammation, induction of cardiomyocyte apoptosis and interstitial fibrosis, aberrant signaling of beta-arrestin and epidermal growth factor, inhibition of nuclear topoisomerase II β, induction of DNA damage, disruption of vascular endothelial growth factor signaling, impaired mitochondrial biogenesis, and calcium overloading [7].

Maintaining homeostasis in myocardial tissue depends on mitochondria, and a decline in mitochondrial function ultimately results in the demise of cardiomyocytes and endothelial cells, which subsequently impairs cardiovascular function. Antiretroviral nucleoside reverse transcriptase inhibitors, such as zidovudine, can induce cardiomyopathy by inhibiting DNA polymerase-gamma and promoting mitochondrial DNA mutations, both of which are detrimental to cardiac mitochondrial function. It is possible to classify cardiac adverse effects into two overarching categories: structural and functional. Significantly impaired functionality can be entirely isolated from structural impact, particularly during the initial phases. Several major structural proteins that modulate cardiac muscle contractility are damaged by anthracyclines, including titin, the myofilament-forming protein that controls cardiac function and is implicated in systolic and diastolic dysfunction, in addition to their functional deterioration [8].

Furthermore, it is essential to note that the susceptibility to chronic anthracycline-induced cardiotoxicity varies significantly between individuals. It has been hypothesized that genetic variants may influence the likelihood of developing this adverse effect. Several candidate genes associated with anthracycline metabolism, free radical detoxification, or variations in body iron levels may play a role. Genetic testing was advised as a preventive measure against such adverse effects [9].

Anthracyclines have a higher propensity to induce irreversible microstructural damage to cardiomyocytes, which results in necrosis and apoptosis (type 1 drug-induced cardiotoxicity). Significantly, biological drugs that target proteins involved in regulating cancer cell proliferation, which are also vital for maintaining cardiovascular homeostasis, are associated with reversible (type 2) cardiotoxicity. This toxicity can be resolved either upon therapy completion or even during its course and overlap and addition between types may occur when multiple potentially cardiotoxic drugs are used. It is worth noting that specific authors classify reversible cardiotoxic adverse effects induced by medicines as type 1, whereas irreversible ones are classified as type 2 [10].

1.3 Features

A multitude of chemotherapy medications have been linked to detrimental cardiovascular effects, including arrhythmias, conduction disturbances, myocardial ischemia, hypertension, and thromboembolic complications. Anthracyclines have been the subject of the most extensive

research among these medications due to their capacity to induce cardiac dysfunction, specifically heart failure. Chemotherapy-induced cardiotoxicity (CTX) can also be caused by other categories of chemotherapeutic agents, including antimetabolites (5-fluorouracil, capecitabine), antibiotics (mitomycin, bleomycin), alkylating agents (cyclophosphamide, ifosfamide), platinum agents, and antimicrotubular agents (taxanes) [2] Table (1) shows the drugs , principal characteristics, and mechanisms of non-anthracycline chemotherapy-induced cardiotoxicity .

Table 1: Principal characteristics and mechanisms of non-anthracycline chemotherapy-induced cardiotoxicity [11].

Drugs	Cardiotoxicity	Mechanisms
Alkylating agents (cyclophosphamide, ifosfamide)	• Acute myopericarditis • Cardiac tamponade • Arrhythmias • Heart failure (high dose)	• Direct endothelial injury • Oxidative stress • Mitochondrial damage • Glutathione S-transferase P (GSTP) deficiency . • Reduced expression of heart fatty acid-binding protein and carnitine palmitoyl transferase
Platinum	• Electrocardiographic changes • Angina • Arrhythmias • Myocarditis • Cardiomyopathy • Congestive heart failure • Acute myocardial infarction • Hypertension • Hypotension • Increased thrombotic events	• Direct myocytes injury • Oxidative stress • Mitochondrial ultrastructural abnormalities • Platelet activation and aggregation
Antimetabolites (fluorouracil and capecitabine)	• Angina-like chest pain • Myocardial infarction • Arrhythmias • Ventricular tachycardia • Heart failure • cardiogenic shock • QT prolongation with torsade de pointes	• Coronary artery thrombosis • Arteritis • Vasospasm • Oxidative stress in myocardiocytes and endothelial cells • Citrate accumulation. • Krebs cycle alteration

Antibiotics (mitoxantrone, bleomycin, mitomycin C)	• Arrhythmias • Diastolic dysfunction	• Oxidative stress • Damage to mitochondrial respiratory chain. • Impaired energy metabolism
Antimicrotubular agents (paclitaxel and docetaxel)	• Ischemic heart disease • Chronic heart failure • Myocardial ischemia • Bradycardia • Atrioventricular block • Left bundle branch block. • Ventricular tachycardia • Ischemic cardiac events	• Damage to Purkinje system or autonomic control. • Induction of histamine release • Enhanced metabolism of doxorubicin toxic species

Type I antineoplastic agents induce irreversible cardiotoxicity, whereas type II reversible cardiotoxicity is induced at varying intensities and levels. CTX induced by type I chemotherapy is distinguished by its ability to induce cardiomyocyte damage. Concerning its onset, CTX has the potential to manifest as acute, subacute, or chronic. Irregularities in ventricular repolarization and QT-interval changes on electrocardiograms, arrhythmias of the ventricle and supraventricular, acute coronary syndromes, pericarditis, and myocarditis-like syndromes distinguish acute or subacute CTX. These manifestations may occur between the commencement of treatment and two weeks after treatment discontinuation. On the contrary, chronic CTX can be classified into two subtypes according to the emergence of clinical symptoms: early, which occurs no later than one year after chemotherapy concludes, and late, which occurs beyond one year after chemotherapy [12].

Chronic CTX is characterized most frequently by asymptomatic systolic and diastolic LV dysfunction, which may progress to dilated cardiomyopathy. Acute injuries, such as ischemia, may cause chronic toxicity in the form of left ventricular systolic dysfunction, and non-anthracycline chemotherapy may induce these complications hours or days after treatment initiation. Furthermore, existing evidence suggests that the utilization of non-anthracycline chemotherapeutics is concurrently linked to a lifelong risk of CTX [13].

2. Cardiac biomarkers

Biomarkers are quantifiable biological variables offering impartial insights into typical and abnormal biological processes. The term "biomarkers" is currently used to refer to biochemicals found in the body's circulating serum and plasma. Beyond what is presently possible with pre-existing assays, the ideal biomarker should enhance clinical outcomes by facilitating improved risk stratification, diagnostic certainty, and disease progression and treatment response monitoring. Additionally, the biomarker assay should produce accurate and replicable outcomes characterized by a swift response time and a reasonable price [14].

Among serum biomarkers validated in detecting cardiotoxicity, natriuretic peptides (NPs) and troponin are the most used in clinical practice [15,16]. NPs, including B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), are quantitative and qualitative markers for the presence and severity of hemodynamic cardiac stress as in heart failure [17]. NPs can also be utilized to detect acute cardiotoxicity because they increase within 24 hours after exposure to anthracycline treatment [18, 19]. Short-term changes in high-sensitivity cardiac troponin (hs-cTn) concentrations can distinguish acute disease from chronic cardiomyocyte distinguish [20]. Chronic cTn elevation can be associated with the presence of comorbidities such as chronic renal disease, diabetes mellitus, serious left ventricular hypertrophy, and heart failure [21], accounting for the limited specificity of high-sensitive troponin assays . According to Lyon et al. and based on our experience, serial NPs and hs-cTn assessments should be performed in all patients with cancer at risk of cardiotoxicity [22 ,15]. Troponin as a biomarker indicates cardiomyocyte damage [23, 24, 25] In contrast, BNP is a measure of increased cardiac strain [23, 26]. NPs are strong predictors of long-term cardiovascular dysfunction in asymptomatic patients [27]. Other biomarkers provide information on acute injury but may not remain elevated in the long-term.

Several novel biomarkers (e.g., myeloperoxidase, high-sensitivity C-reactive protein, sFlt-1, placental growth factor, growth differentiation factor-15, galectin-3, arginine, heart type of fatty acid binding protein, glycogen phosphorylase BB) have been studied to detect earlier or subclinical cardiotoxicity and initiate cardioprotective strategies beyond the prediction currently provided by cTn and NPs [28,29]. Furthermore, immune system indicators (such as immunoglobulin E) may aid in identifying patients at high risk for doxorubicin and trastuzumab cardiotoxicity [30]. Finally, recent studies in breast cancer patients have highlighted microRNAs as a possible biomarker in

detecting cancer drug-induced cardiotoxicity [31]. (Table 2)[32] shows Comparison of main characteristics of biomarkers potentially employed in cardiotoxicity detection.

Table 2 Comparison of main characteristics of biomarkers potentially employed in cardiotoxicity detection. [32]

Biomarkers	Disease	Characteristics
cTn	ACS, HF, PE	Cardiac-specific structural proteins that form the contractile apparatus of cardiomyocytes.
BNP and NT-proBNP	HF, PE	Cardiomyocytes release an inactive form (prohormone) of BNP in response to increasing transmural tension and neurohormonal stimulation (most notably noradrenaline and angiotensin II).
Myeloperoxidase	ACS	Released into extracellular fluid in response to inflammatory events
High-sensitivity C-reactive protein	Aortic dissection, ACS	Marker for the progression of false lumen thrombosis
sFlt-1	Atherosclerotic cardiovascular disease	Markers for inflammation, endothelial function, and myocardial stress or injury
Placental growth factor	ACS	Endothelial cell mitogen; can also serve as a proinflammatory cytokine.
Growth differentiation factor-15	Myocarditis	Marker of extracellular matrix degradation
Galectin-3	HF	Marker of cardiac and vascular fibrosis

Arginine	HTN, PH, atherosclerosis, and vasospasm Endothelial dysfunction	Arginine is the primary source of NO production via NOS.
H-FABP	ACS, HF, arrhythmia, PE	A dominant isoform exists in the heart and skeletal muscles, acting as a sign of continuing myocardial injury.
Glycogen phosphorylase BB	ACS	Provide fuel for the energy source needed for cardiac contraction.
Immunoglobulin E	Cardiac dysfunction, HF	Dysregulation of the inflammatory response could worsen cardiac remodeling and cardiac damage.
microRNAs	ACS	Non-coding RNAs suppress mRNA translation or stimulate its destruction; involved in all cardiac activities, including electrical signal conductivity, heart muscle contraction, and growth.

Abbreviations: ACS; acute coronary syndrome; BNP, B-type natriuretic peptide; cTn, cardiac troponins, cTn; HF, heart failure; H-FABP, heart-type of fatty acid binding protein; HTN, systemic arterial hypertension; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PE, pulmonary embolism; PH, pulmonary hypertension; sFlt-1, soluble Flt-1, TTS, Takotsubo syndrome.

Currently, definitive guidelines concerning biomarkers for detecting cancer drug-induced cardiotoxicity (CDIC) and cancer radiation-induced cardiotoxicity (CRIC) do not exist. The lack of comparability and inconsistency in trial results is primarily attributable to the absence of standardized trial methodologies.

The trials are highly heterogeneous regarding malignancy categories, cancer treatment schedules, and the definition of cardiotoxicity. In addition, distinct biomarker assays with varying threshold

values are utilized in each trial. Biomarker samples are collected at various frequencies and time intervals by the treatment protocol.

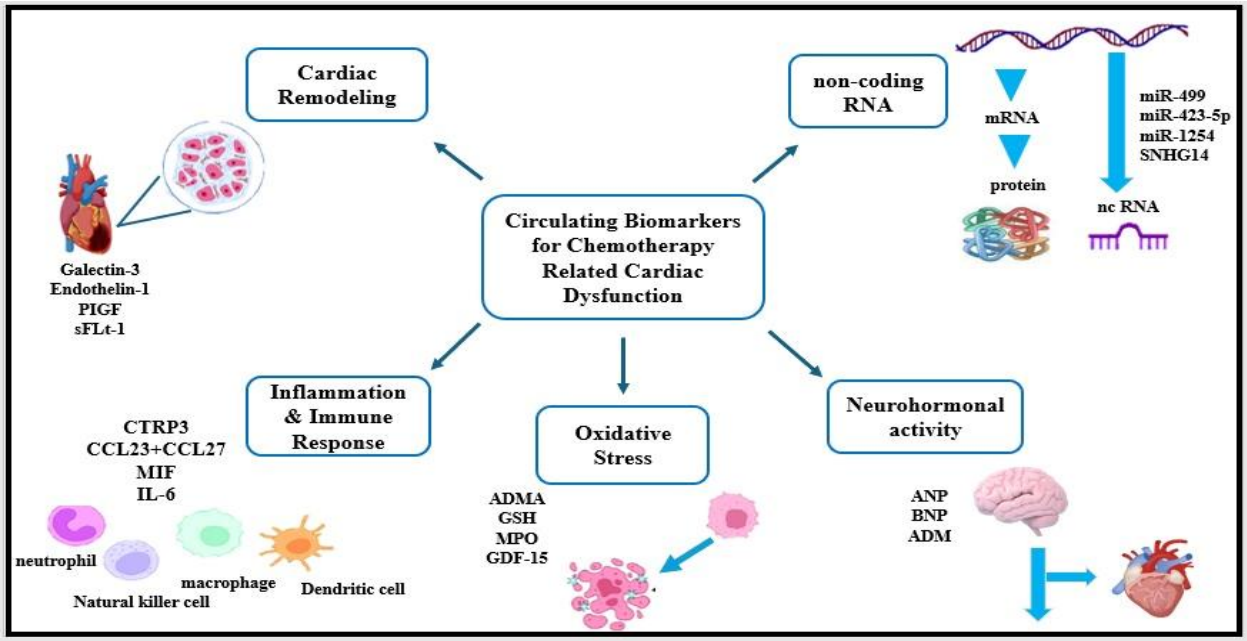

Fig. 1: Cardiotoxicity mechanisms and illustrative instances of correlated biomarkers. [33].

3. Current Recommendations for Biomarker Utilization

In light of the growing body of evidence in cardio oncology, reputable scientific organizations have issued papers and consensus statements concerning cardiotoxicity. Mainly, recommendations about surveillance throughout treatment are provided. According to the 2014 consensus statement of the American Society of Echocardiography (ASE), elevated troponin levels in patients undergoing chemotherapy that has the potential to cause cardiotoxicity may serve as a sensitive indicator for early detection of toxicity. In contrast, natriuretic peptides (NPs) may exhibit reduced consistency in this regard. Additionally, the ASE document highlights the constraints, such as the unpredictability of biomarker measurement timing and optimal cutoffs. The ASE advises that baseline serum cardiac troponin (cTn) measurement be performed when initiating chemotherapy regimens associated with type I toxicity or trastuzumab (associated with type II toxicity). This level should be used with global longitudinal strain and LVEF to initiate cardiology consultation [34].

To detect early cardiac injury, the European Society of Cardiology consensus asserts that cardiac biomarkers may be considered for use during chemotherapy, and the same assay should be utilized for screening throughout the treatment pathway. This statement further recognizes that the available evidence is inadequate to establish the importance of minor increases in detectable biomarkers or the discrepancies that may arise from utilizing different assays. In addition, they assert that biomarkers cannot be relied upon to predict clinically significant late effects of cancer therapy. It is critical to remember that while both societies have formulated consensus statements regarding this subject matter, they are currently unable to establish comprehensive guidelines. This is due to the limited number of studies and relatively small sample sizes devoted to biomarkers and cardio-oncology. Implementing routine troponin testing in the outpatient setting would necessitate establishing a comprehensive system that encompasses a system-level comprehension of the function of testing [35].

As an illustration of the complementary function of biomarkers for surveillance during chemotherapy, the authors included a generalized pathway (Fig. 2). Nevertheless, it is of the utmost importance to prevent excessively aggressive investigations and incorrect diagnoses of patients who are routinely monitored for cardiotoxicity or undertaking risk assessment [36].

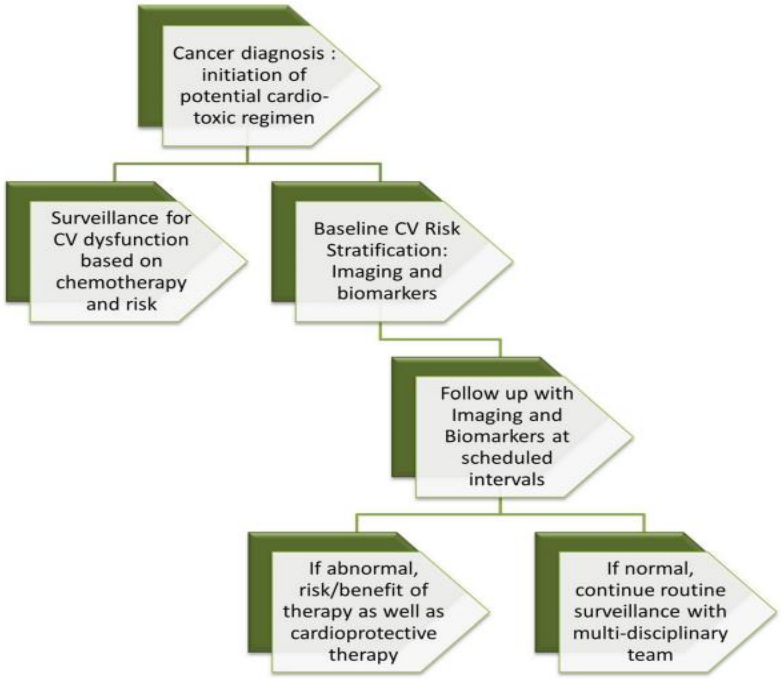

Fig. 2 A multidisciplinary pathway for initiating and monitoring cardiotoxicity that uses routine imaging and biomarkers [36].

Nevertheless, there is a shortage of evidence demonstrating the efficacy of biomarker surveillance among cancer survivors, specifically among those who have endured pediatric cancers. A review of the evidence regarding biomarker surveillance in childhood cancer survivors was conducted for the 2015 International Late Effects of Childhood Cancer Guideline Harmonization Group report. The report concluded that there was insufficient evidence to support the diagnostic value of troponin T and I, NPs, and NPs testing at the Level B level for detecting asymptomatic cardiomyopathy. Furthermore, the report found no evidence to suggest that screening with biomarkers was cost-effective. Therefore, it is not advisable to rely solely on biomarkers for cardiomyopathy surveillance in this population, notwithstanding the potential for long-term cardiotoxicity resulting from anthracycline and radiation dose exposure. However, the report mentioned that it might be rational to combine imaging studies with biomarkers when there is a high suspicion of symptomatic cardiomyopathy or when primary surveillance involves survivors with equivocal cardiac function . Furthermore, there is a notable dearth of evidence about long-term biomarker surveillance in adult cancer survivors, which necessitates additional research [37].

4. Natriuretic peptides

The ventricles secrete brain natriuretic peptide (BNP) and NT-proBNP, an inactive amino acid fragment located at its N-terminus, in reaction to volume excess and wall stress. BNP induces natriuresis and diuresis to sustain euvolemia. The measurement of natriuretic peptide levels in patients with heart failure is currently advised due to the diagnostic, therapeutic, and prognostic value it provides [38].

4.1 Role of natriuretic peptides in anthracycline-induced cardiotoxicity

After troponin, natriuretic peptides are the biomarkers investigated most frequently in the context of CRIC. Multiple studies have demonstrated that they exhibit greater sensitivity as indicators of cardiotoxicity compared to echocardiography. NT-proBNP was substantially elevated at various time points following the conclusion of chemotherapy in a prospective study by De Iuliis and

colleagues, whereas LVEF remained unchanged. Additionally, the authors demonstrated that NT-proBNP predicted one-year mortality [39].

According to another study, a persistent elevation of NT-proBNP early after high-dose chemotherapy was significantly associated with the development of left ventricular systolic and diastolic dysfunction at one-year follow-up, according to another study. An elevation in NT-proBNP levels during the first ninety days of treatment in 205 children with acute leukemia who were administered doxorubicin was suggestive of cardiac dysfunction, as confirmed by echocardiography four years later [40].

In 109 patients diagnosed predominantly with sarcoma and lymphoma, the predictive value of cardiotoxicity was examined via serial BNP measurements taken before and following each cycle of anthracycline therapy. Significantly increased levels of BNP were observed in patients who experienced patient-defined cardiac events (asymptomatic left ventricular dysfunction, symptomatic heart failure, symptomatic arrhythmia, acute coronary syndrome, or sudden cardiac death) prior to and subsequent to each cycle of anthracycline therapy, in comparison to patients who did not experience these events. Following follow-up, cardiac event survivors tended to have a decreased LVEF [41].

4.2 Role of natriuretic peptides in cardiotoxicity associated with other cancer therapies.

Asymptomatic cardiotoxicity in 43 patients (27%) who received tyrosine kinase inhibitors and other targeted therapies for metastatic renal cell carcinoma and an elevated NT-proBNP level or LVEF impairment was observed in a single-center study comprising 159 patients. A reduction in LVEF was observed in twelve out of the 38 patients with elevated NT-proBNP levels. The first treatment cycle posed the most significant risk of left ventricular dysfunction in an additional cohort of patients treated with sunitinib for metastatic renal cell carcinoma. Upon completion of the initial treatment cycle, the LVEF decreased by 1.9% from baseline, which was statistically significant. However, this decline lacked clinical significance and was only temporary, as appropriate cardiac therapies were implemented after that. Throughout sunitinib treatment, no statistically significant alteration was observed in the mean BNP level from baseline [42].

It has also been reported that patients undergoing thoracic irradiation have elevated natriuretic peptide levels, which may indicate cardiotoxicity before LVEF. At six months post-irradiation, patients who underwent radiotherapy for left-sided breast cancer exhibited considerably elevated levels of NT-proBNP in comparison to those who did not undergo radiotherapy.

An even stronger correlation was observed between elevated concentrations of cardiac irradiation and natriuretic peptide elevation [43].

4.3. Role of natriuretic peptides in cancer survivorship

Troponin appears to have limited utility in the long-term surveillance of cancer survivors. As they have been linked to increased left ventricular dimensions and echocardiographic characteristics of systolic and diastolic dysfunction, brain natriuretic peptides may serve as potential early indicators of late cardiotoxicity in cancer survivors [44].

4.4. The cost-effectiveness of incorporating BNP measurements into routine oncological care.

There are several studies that demonstrate the cost effectiveness of BNP . Aziz Rezapour et al indicated that mean Quality-adjusted life-years (QALYs) and cost were estimated to be 2.18 QALYs and $1835 for BNP and 2.07 and $2376 for standard clinical assessment, respectively. BNP was more effective than traditional clinical assessment in terms of cost savings and increased QALYs. BNP was also 85% more cost-effective than routine clinical assessment if the willingness to pay threshold is higher than $20,800/QALY gained.

According to the findings of the current study, assessing BNP levels is definitely good value for money. It lowered expenses and enhanced QALYs when compared to normal clinical assessment. Based on the findings of this study, it is advised that the BNP test be covered by insurance due to its high cost for heart failure patients . Furthermore, it was recommended when formulating professional standards for the diagnosis of cardiotoxicity [45]

Another study found that screening with BNP followed by echocardiography in those with an abnormal results was cost effective for 60-year-old men and potentially for women. Screening all patients with echocardiography was expensive and relying just on BNP to choose treatment , resulted in higher costs and worse outcomes than the sequential BNP-echocardiography strategy. Overall, screening with BNP followed by echocardiography is expected to be affordable for patient groups with at least a 1% prevalence of moderate or greater LV systolic dysfunction [46]

4.5.Limitations of natriuretic peptides

Certain researchers are unable to establish a correlation between cardiotoxicity and natriuretic peptides. Similar to the troponin trials, inconsistent natriuretic peptide trial results can be attributed to a retrospective design, a small sample size, and the absence of standardized biomarker reference ranges. Angiotensin II levels are elevated in females, and the elderly, and renal dysfunction exacerbates natriuretic peptide concentrations. Recent evidence also indicates that cancer-associated inflammation may potentially elevate BNP levels; patients with metastatic disease exhibit considerably higher BNP levels compared to those without metastatic involvement. These confounding variables must be considered when interpreting the results [5].

5. Prevention and treatment of cardiotoxicity

A number of review articles have recently been published, aiming to improve the cardiologic follow-up of cancer patients and shed light on the underlying mechanism of anticancer drug cardiotoxicity. Proficient identification of susceptible patients, formulation of preventive measures, and prompt intervention in cases of cardiotoxicity should comprise the optimal management approach [47].

5.1 Identification of the high-risk population

The incidence of pre-existing cardiac disease in cancer patients was 9.3%, which indicates that this risk is underestimated. Several cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, and electrolyte imbalances, can be corrected and treated before initiating anticancer therapy. These conditions should then be closely monitored throughout treatment. Cardiac

specialists should evaluate patients who have pre-existing cardiac disease or are taking medications that may cause QT prolongation [48].

5.2 Monitoring cardiac function

In spite of the lack of consensus regarding the optimal method for assessing cardiotoxicity, periodic evaluation of LVEF should be conducted prior to, during, and subsequent to treatment with cytotoxic or targeted compounds known to induce HF in order to detect subclinical cardiac injury. Periodic electrocardiograms should be obtained for QTc monitoring, particularly in patients who are at risk. It is advisable to conduct cardiac surveillance on a predetermined schedule, including a baseline ECG seven days after treatment initiation and periodic ECGs after any dose adjustments. Primary research interest is devoted to developing improved biomarkers for identifying patients at high risk of cardiotoxicity and to the integration of various methods for cardiologic monitoring [49].

5.3 Development of cardioprotective drugs

Most randomized trials involving cardioprotective agents and anthracycline-treated patients have methodological flaws. Dexrazoxane, an ethylenediaminetetraacetic-like iron chelator, was found to have a statistically significant advantage over the control group regarding the incidence of HF in six randomized controlled trials. Response rate and survival did not differ significantly between the dexrazoxane and control groups. Dexrazoxane treatment should be limited to patients diagnosed with metastatic breast cancer who have undergone sustained anthracycline-based therapy and have been administered a minimum of 300 mg/m2 of anthracycline, as recommended by the American Society for Clinical Oncology (ASCO) [3].

In a randomized trial, patients undergoing high-dose chemotherapy and exhibiting elevated serum troponin I levels were administered ACE inhibitors. HF was not observed in any of the 56 patients administered the ACE inhibitor, whereas it developed in 24% of the control patients. Ongoing research focuses on the development of alternative endothelial or cardiomyocyte protective agents to mitigate the cardiotoxicity of anticancer medications while maintaining their antitumor efficacy [50].

5.4 Cardiotoxicity assessment in drug development

According to FDA and EMEA guidelines, every phase I clinical trial incorporates a comprehensive cardiac monitoring protocol. An additional objective is the detection of off-target toxic effects caused by kinase inhibitors and the creation of novel pharmaceuticals that stimulate those off-target kinases. An instance of this is the effective redesign of imatinib for treating GIST, which reduced its cardiotoxic effects [51].

5.5 Early management of cardiotoxicity

Antineoplastic drugs should be discontinued during a cardiovascular event, such as prolonging the QTc by more than 500 milliseconds or a significant decrease in LVEF. Additional factors that may have contributed to this cardiovascular incident, including electrolyte imbalances or coronary disease, warrant investigation and intervention [52].

Early interventional treatment with ACE inhibitors and b-adrenergic blocking drugs has proven to be effective in the management of LVEF dysfunction in adult patients who have decreased LVEF without an explicit etiology attributable to anthracycline therapy. The effectiveness of ACE inhibitors in cancer patients was assessed in a single-center study, which determined that this therapeutic modality promotes left ventricular elemental function (LVEF) restoration and is associated with a reduction in cardiac events [53].

6. Conclusion

In conclusion, these biomarkers have shown predictive value for both short-term and long-term cardiac dysfunction, surpassing traditional echocardiographic methods .Their elevated levels can precede clinical symptoms and echocardiographic changes, offering a crucial window for early intervention. There is a hope that the use of biomarkers can help in identifying patients undergoing treatment who are at high risk for cardiotoxicity . The detection of BNP levels are more cost effective than traditional clinical assessment. It lowered expenses and enhanced QALYs when

compared to normal clinical assessment. Given their proven association with adverse cardiac events and potential to guide therapeutic decisions, incorporating natriuretic peptide measurements into routine oncological care could significantly improve cardiovascular outcomes in cancer patients and survivors. This article recommended that patients susceptible to cardiotoxicity detected by BNP should take cardioprotective drugs such as ACE inhibitors and b-adrenergic blocking drugs prior to chemotherapy. The ideal management approach should include susceptible patients, preventive measures, and prompt intervention in cases of cardiotoxicity.

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● **Conflict of Interest**

A declaration of conflict of interest.

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