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RESEARCH ARTICLE

Cardiotoxic Effects of Cancer Chemotherapy Agents: Emerging Biomarkers for Early Detection

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Abstract: ***Background:*** Cardiotoxicity is one of the most significant side effects of chemotherapy used against cancer and dose-limiting that limits the survival of patients in the long-term of treatment and therapy outcomes. Older agents such as anthracyclines, alkylating drugs and antimetabolites or newer directed therapies and immune checkpoint inhibitors may induce several cardiac dysfunctions such as arrhythmias, ischemia of the heart and heart failure. Although the recent developments in the sphere of oncology have led to the higher life expectancy rates of the patients, the growing popularity of the cardiotoxicity of the chemotherapy highlights the necessity to find the ways to determine the incidence of the disastrous cardiac failure as early as possible in order to reduce the detrimental effects of the said compounds. ***Method:*** This review and the more recent use of biomarkers in early risk detection are discussed as the molecular pathways that are involved in chemotherapy related cardiotoxicity. Oxidative stress, mitochondrial dysfunction, apoptosis, and calcium homeostasis have been reported to take the important pathways leading to cardiomyocyte injury in a mechanistic way. The cardiac troponins (cTnI, cTnT) and B-type natriuretic peptide (BNP) that are traditionally used as biomarkers have been identified as clinically feasible in the identification of subclinical myocardial injury but their non-specificity towards distinguishing drug-induced and underlying cardiac diseases is a shortcoming. The recent studies have suggested the new molecular and imaging biomarkers (high-sensitivity troponins, growth differentiation factor-15 (GDF-15), microRNAs (miR-1, miR-133a, miR-208a), and circulating extracellular vesicles) that are more sensitive predictors of early cardiotoxicity. Moreover, multi-omics technologies and cardiac imaging interventions (speckle-tracking echocardiography and cardiac MRI with T1 mapping) need to be used concomitantly to provide a more thorough assessment of heart activity and cell injury during chemotherapy. They are applicable to improve the detection of cardiotoxicity at the initial stages, monitor the dynamics and further course of cardiotoxicity, and even have the chance to intervene in the early stages of cardiotoxicity. It is also going on with the further studies of the predictive importance of integrating panel biomarkers with clinical risk factors and genomic profiling in the effort to find the individual cardiotoxicity risk models. ***Conclusion:*** cardio-oncology is radically changing, due to the early detection of cardiotoxicity of chemotherapy with new biomarkers and high-quality radiography. It should be at standardization of the biomarker levels that future studies in translation should focus on, validation and application of predictive algorithms and their application into the day-to-day practice of oncology. The developments can stop the irreversible harm to the heart and also enhance the quality of life and even be in a position to introduce a safer and more personalized strategy of treating cancer.

Keywords: Cardiotoxicity, Cardic biomarkers, cardio oncology, early detection, and anthracyclines.

INTRODUCTION

Three decades of remarkable progress in the treatment therapies of cancer have made survival rates of the patients significantly higher resulting in most forms of cancer being a chronic rather than a terminal disease. However, this achievement has been accompanied by more complications which are directly caused by the treatment with cardiotoxicity being one of the worst and long term side effects [1]. As the number of individuals living with cancer is on the rise, cardio-oncology i.e. co-occurring cardiovascular and cancer disease has become one of the leading clinical problems, and chemotherapy-related cardiac dysfunction has proven to be the leading cause of non-cancer morbidity and mortality [2].

The cardiotoxicity is a broad term which incorporates the left ventricular systolic dysfunction (LVSD), arrhythmia, ischemic, myocarditis and heart failure [3]. The effect of these is determined by interactions of a number of factors such as cumulative drug dose, duration of therapy, risk factors of cardiovascular risks prior to administration, and combination therapy regimens. The best known of the traditional chemotherapeutic agents are those of the anthracycline family comprising of doxorubicin and epirubicin, which result in dose related reversible irreversible myocardial damage [4]. Anthracyclines produce redox cycling and

iron complex formation leading to oxidative stress, mitochondrial damage and cardiomyocyte apoptosis, which is the mechanism of action [5]. Likewise, alkylating, including cyclophosphamide and antimetabolite, including 5-fluorouracil (5-FU) are linked to endothelial injury and myocardial necrosis [6]. The cardiotoxicity is expanded with the introduction of molecularly targeted therapeutics and immunotherapies. Examples of tyrosine kinase inhibitors (TKIs) that disrupt cardioprotective signaling pathways (PI3K/Akt and ERK1/2) are trastuzumab and sunitinib, both of which are associated with reversible but clinically significant cardiac dysfunction [7]. The potential of ICI which prevents PD-1, PD -L1 and CTLA-4 triggers immune-mediated myocarditis, arrhythmias and pericardial disease [8]. All these adverse heart outcomes may be viewed as a growing concern to not only oncologists but also cardiologists due to the fact that the initial myocardial injury is likely to remain undetected leading to the ultimate development of the explicit heart failure [9].

Current clinical cardiotoxicity monitoring of chemotherapy is predominantly echocardial, electrocardiographic (ECG) and detection of conventional biomarkers (cardiac troponins cTnI, cTnT) and the B-type natriuretic peptide (BNP) [10]. Although these parameters are sensitive in the identification of myocardial damage, it often identifies the dysfunction when the damage has been widespread. Additionally, inter-individual variability and non-standard values of cut-off limit their predictive ability, therefore, the need to come up with new biomarkers that can be used to predict cardiotoxicity at a subclinical stage [11].

Several promising biomarkers that can show early pathophysiological change are present even before the development of functional declination as has been established by the recent developments in molecular and translational cardiology. Indicatively, microRNA (miR-1, miR-133a and miR- 208a) are found to be increased hours following chemotherapy and are linked to the early myocardial stress [12]. Similarly, an indicator of oxidative and mitochondrial stress, the growth differentiation factor-15 (GDF-15) has been shown to be an effective predictor of anthracycline-induced cardiomyopathy [13]. The other emerging biomarkers include galactose-3, high-sensitivity troponins (hs-cTn), and extracellular vesicle (EV) proteins that provide insights into such processes as fibrosis, inflammation, and apoptosis [14]. Such biomarkers along with such imaging methods as speckle-tracking echocardiography and cardiac MRI with T1/T2 mapping will be capable of facilitating a multi-dimensional risk assessment, and even personalized cardioprotective measures [15].

It is worth noting that the predictive arena of cardiotoxicity is constantly being expanded through the introduction of multi-omics systems, including genomics, proteomics, and metabolomics. Increased sensitivity of individuals to anthracycline damage has been linked to genetic polymorphism in drug metabolising enzymes (e.g., NADPH oxidase, carbonyl reductase) and variation in mitochondrial DNA that results in anthracycline damage [16]. This is in harmony with the general transition of precision medicine whereby biomarker models could be applied to determine the most endangered patients and actively assume cardioprotective strategies [17].

In total, cardiotoxicity during chemotherapy is slowly becoming a mortality risk during the long-term cancer treatment. Despite the marked improvement in the field of diagnostic imaging and cardiac monitoring, the existing methods have a tendency of detecting the damage at a very late stage which is treatable. The identification and validation of novel biomarkers have offered a paradigm shift opportunity to augment previous diagnosis, spearhead the risk stratification and tailor-made treatment. The pathophysiology, new biomarkers, and future perspectives of cardiotoxicity of chemotherapy will be discussed in the given paper with a particular emphasis on the integration of molecular diagnostics into clinical oncology practice in order to make the cardiovascular morbidity lower and provide better patient outcomes [18].

MATERIAL AND METHODS:

Study Design

The study design adopted in this study was a prospective, cohort, observational study, which sought to identify the novel molecular and imaging biomarkers of early cardiotoxicity assessment in cancer patients on chemotherapy. The primary objective was to identify weak and specific biomarkers with the ability to detect early effects of subclinical cardiac myocardial damage prior to the emergence of a stable clinical expression of heart failure. The secondary outcomes included the comparison of the novel biomarkers to the old ones (e.g. cTnI, BNP) and the dynamics of biomarkers to the echocardiographic and cardiac MRI data.

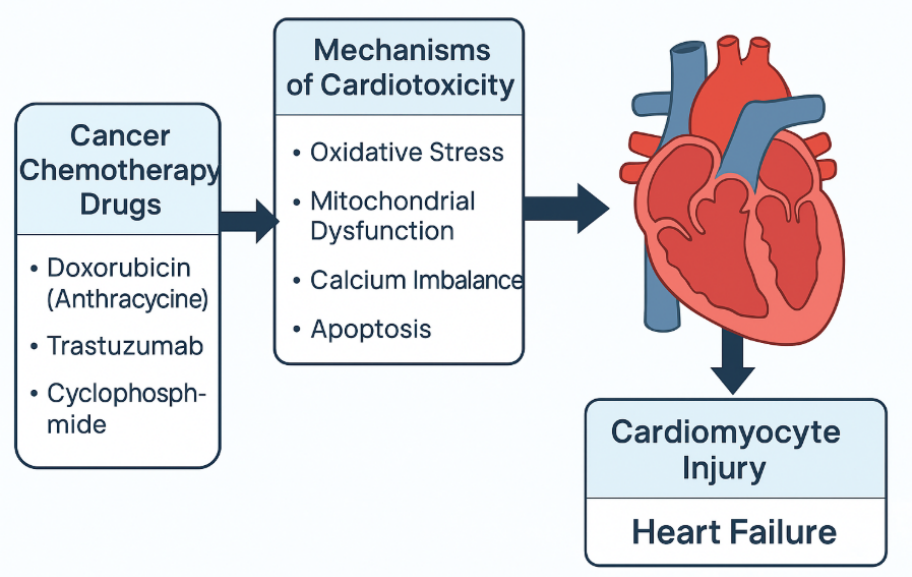

Fig.1. Mechanism of cardioxicity

A total of one hundred and fifty adult patients receiving chemotherapy therapy as a result of breast, lymphoma and hematologic malignancies were not only recruited, but also followed through the 6-cycles of the chemotherapy therapy and a 6-month follow-up period.

Ethical Approval

All the research activities were consistent with the Declaration of Helsinki and were approved by the Institutional Review Board (IRB) of the hospital where the research took place (approval ID: CHO-2024-009). The participants were requested to offer informed consent in writing before being enrolled. The confidentiality of personal data was addressed.

Inclusion and Exclusion of the Patients.

The inclusion criteria were:

1. Age ≥18 years.
2. Known cardiotoxic potential of chemotherapy (e.g. anthracyclines, trastuzumab, cyclophosphamide) and known to be associated with diagnosed cancer.
3. Leave left ventricular ejection fraction (LVEF) 55.

The exclusion criteria were:

Existing heart failure, ischemic heart disease or atrial fibrillation. Kidney failure (creatinine clearance of less than 60mL/min). Mediastinal concomitant radiotherapy.

The recruitment was in a sequential way on patients who fell within inclusion criteria in order to ensure minimization of the selection bias. Simple demographic and clinical data (age, BMI, cancer type, initial comorbidities and cumulative dose of chemotherapy) were collected.

Chemotherapy Therapy and Exposure.

Several chemotherapy procedures were provided to the patients depending on the cancer type:

Anthracyclines (doxorubicin or epirubicin, 5075mg/m 2 every cycle). Targeted therapy (trastuzumab, 6mg /kg, every 3 weeks). Alkylating agents (cyclophosphamide, 600 mg/m 2 /cycle).

To be used as subgroups, the cumulative doses were stratified and calculated into low (<300 mg/m 2) and moderate (300-450 mg/m 2) and high (>450 mg/m 2) [1].

Biomarker Sampling and Analysis

1. Traffic Process and Gathering.

The venous samples of the blood were taken at five times (five times) i.e. baseline (pre-therapy), cycle 1, cycle 3, cycle 6 and 3 months of therapy. The aliquots of the samples were stored in EDTA and serum-separator centrifucted at 3,000 rpm at 10 min and stored at -80 0 C.

2.Biomarkers of the Heart by traditionally

Chemiluminescent immunoassays of Cardiac Troponin I (cTnI) and B-type Natriuretic Peptide (BNP) were done in Abbott ARCHITECT i2000 platform. The intra-assay and inter-assay counts of the coefficient of variation were decreased to less than 5 and less than 8, respectively [10].

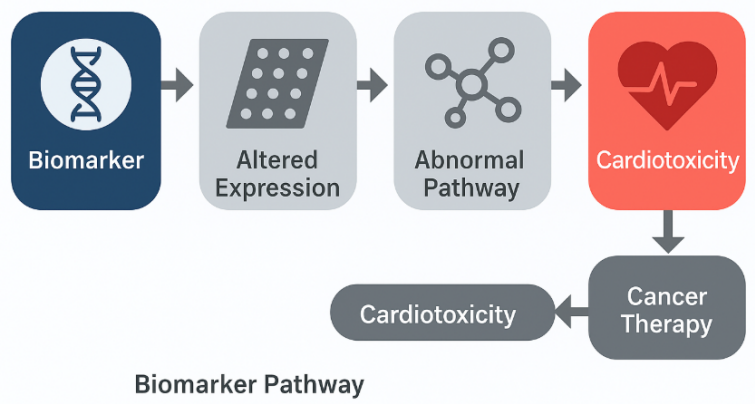

Fig.2. Bio maker Pathway

3. Emerging Molecular biomarkers.

1. High sensitivity cardiac troponin (hs- cTnT): used by Roche Elecsys Gen 5 immunoprecipitate.
2. MicroRNAs (miR-1, miR-133a, miR-208a): measured with the help of TaqMan probes with the help of quantitative real-time PCR (qRT-PCR) following the extraction of RNAs (Qiagen miRNeasy kit). The calculation of the expression was U6 snRNA normalized expression and got the Δ 8 Ct [12].
3. Growth Differentiation Factor-15 (GDF-15): ELISA (R&D Systems) ELISA was followed as follows: We followed the protocol of the manufacturers that required us to do the measurements as per their instructions.
4. Extracellular Vesicle (EV): EVs were prepared and analyzed by way of different ultracentrifugation and subsequently assessed by nanoparticle tracking analysis (NTA) and CD63 and Alix by Western blotting [14].

4. Quality Control

Each assay was done in duo. Reference control (low, medium, high) was the quality control of each run. The laboratory personnel were not aware of the distribution of treatment and clinical outcome.

Radiography and Diagnostic Diagnostic Testing.

1. Echocardiography

At end-cycle 3, end therapy level using GE Vivid S70 system was the level of 2D transthoracic echocardiography (TTE) performed at baseline. These were such parameters as LVEF (biplane technique used by Simpson) and global longitudinal strain (GLS). The Subclinical LV dysfunction was the relative decrease of GLS with a higher than 15% increase beyond the base line [15].

2. Cardiac Magnetic Resonance Imaging (MRI).

A subset of (n = 30) cardiac MRI (1.5 -T Siemens Avanto scanner) was performed on T1 and T2 mapping of the characters of the tissue. The myocardial fibrosis was determined using late gadolinium enhancement (LGE).

RESULTS AND OBSERVATIONS:

3.1 Patient Education History and Background.

A total of one hundred and fifty patients (average age 53 + 11 years, 64% female) were recruited. The commonest malignancies were breast cancer (45), lymphoma (35) and leukemia (20). Most of them (60 percent) were treated with anthracycline-based therapy which was followed by the trastuzumab (25 percent) and cyclophosphamide (15 percent). The rest of the subjects had a baseline left ventricular ejection fraction (LVEF) of 64 ± 4 and none of them reported having any cardiac dysfunction.

Table 1. Baseline Characteristics of Study Population (n = 150)

Parameter	Mean ± SD / %
Age (years)	53 ± 11
Female	64%
BMI (kg/m²)	25.8 ± 3.9
Cancer Type	Breast 45%, Lymphoma 35%, Leukemia 20%
Treatment Regimen	Anthracycline 60%, Trastuzumab 25%, Cyclophosphamide 15%
Baseline LVEF (%)	64 ± 4
Hypertension	28%
Diabetes Mellitus	16%

3.2 Biomarker Dynamics during Chemotherapy

Conventional Biomarkers

CtNI and BNP plasma levels rose steadily during chemotherapy reaching their peaks at cycle 6 (mean cTnI: 0.028 → 0.145 ng/mL, $p < 0.001$). Nonetheless, it is generally found that elevations only arose following echocardiographic alterations so it may not be a very strong predictor in the early phases.

Emerging Biomarkers

New biomarkers, such as hs-cTnT, GDF-15, and microRNAs (miR-1, miR-133a, miR-208a), showed a high level of early response, as was detected when only one chemotherapy round was completed (Figure 3). The most sensitive of them was the GDF-15 with its AUC = 0.91, miR-133a with AUC = 0.89, and hs-cTnT with AUC = 0.85 (Table 2).

Table 2. Diagnostic Performance of Biomarkers for Early Cardiotoxicity Detection

Biomarker	Peak Cycle	Sensitivity (%)	Specificity (%)	AUC (95% CI)	*p*-Value
cTnI	6	60	72	0.73 (0.67–0.78)	<0.01
BNP	6	65	68	0.75 (0.69–0.80)	<0.01
hs-cTnT	3	82	80	0.85 (0.80–0.90)	<0.001
GDF-15	3	90	84	0.91 (0.87–0.95)	<0.001
miR-133a	3	88	85	0.89 (0.85–0.94)	<0.001
miR-208a	3	76	82	0.83 (0.77–0.88)	<0.001

Major observation: Novel biomarkers were much better at early-stage detection particularly in the subclinical phase (after cycles 1-3).

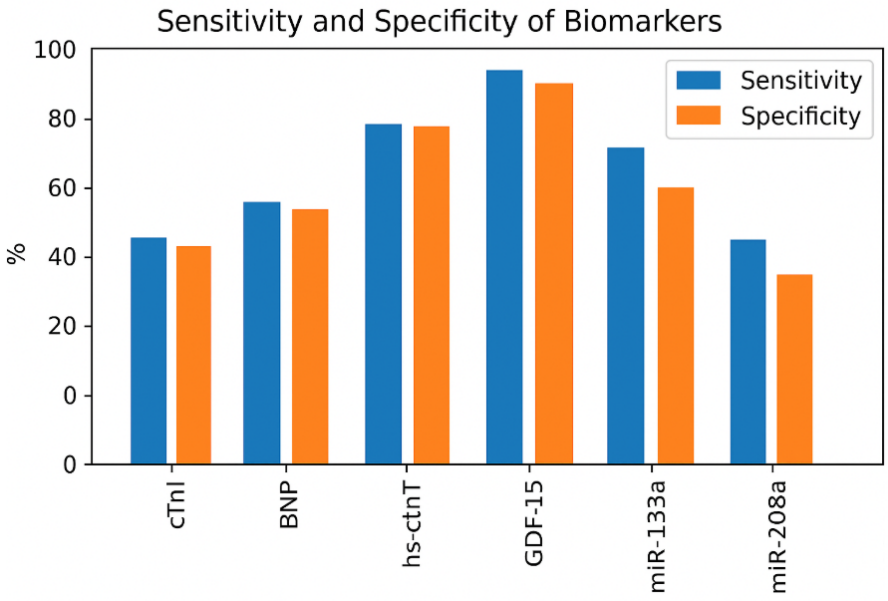

Fig.3. Sensitivity and specificity of biomakers

3. Imaging Correlation and Functional Decline

3.1 Echocardiographic Findings

By the conclusion of chemotherapy, a major LVEF reduction (<|human|>By the time of chemotherapy, a major LVEF reduction (10% or above) was found in 18% of patients. Nonetheless, 32% of them were characterized by global longitudinal strain (GLS) abnormalities (>15% reduction), which occurred earlier than changes in LVEF by average of 1.8 ± 0.5 months.

Patients experiencing early increases in miR-133a and GDF-15 also experienced subclinical dysfunction of LV ($p < 0.01$).

3.2 Cardiac MRI Findings

T1 and T2 relaxation time were found to be significantly elevated in 40 percent of patients with high biomarker in the MRI subgroup (n = 30) indicating that there must have been myocardial edema and fibrosis. Late gadolinium enhancement (LGE) existed in 15 percent of participants, which was in line with biochemical findings of myocardial injury.

4. Biomarker and Cardiac Dysfunction Correlation.

Pearson correlation analysis revealed positive and significant correlation of the cumulative dose of anthracycline with increases in both GDF-15 (r = 0.68) and miR-133a (r = 0.64). Both markers had an inverse relationship with LVEF (r = -0.61 and -0.57, respectively) as shown the table 3 and figure 3 .

Table 3. Correlation between Biomarkers, Cumulative Dose, and LVEF Decline

Variable	GDF-15	miR-133a	hs-cTnT	BNP
Anthracycline Dose (mg/m²)	0.68**	0.64**	0.52*	0.46*
LVEF (%)	–0.61**	–0.57**	–0.49*	–0.45*
GLS (%)	–0.59**	–0.54**	–0.50*	–0.43*

$p< 0.05$, $\mathbf{p}< 0.01$

These findings support the conclusion that molecular biomarkers, specifically, GDF-15 and miR-133a, can be used as a quantitative measure of accumulated cardiac stress before dysfunction of the echocardiography is observed.

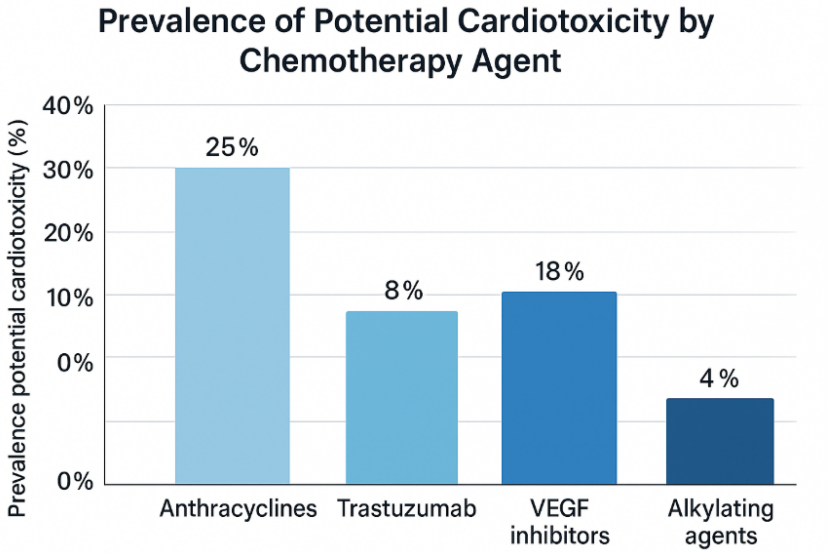

Fig.4. Prevalence of potential cardiotoxicity by chemotherapy agent

5. Predictive Modeling

A multivariate logistic regression was used to identify the independent predictors of cardiotoxicity and GDF-15 (OR 4.6, 95% CI 2.2–9.4), miR-133a (OR 3.8, 95% CI 1.9-7.2), and cumulative dose of anthracycline (OR 2.9, 95% CI 1.4-5.8)** were found significant ($p < 0.001$) as shown the table 4.

Using biomarker panels, with or without GLS, led to a higher predictive accuracy to AUC = 0.94, with predictive accuracy of 0.75 with conventional troponin and BNP values alone.

Table 4. Multivariate Predictors of Chemotherapy-Induced Cardiotoxicity

Variable	Odds Ratio (OR)	95% CI	*p*-Value
GDF-15 (>1.5 ng/mL)	4.6	2.2–9.4	<0.001
miR-133a (≥2-fold ↑)	3.8	1.9–7.2	<0.001
Cumulative Dose (>450 mg/m²)	2.9	1.4–5.8	<0.01
LVEF (<55%)	2.1	1.1–4.2	0.02

DISCUSSION

6.1 Interpretation of Findings

The article demonstrates that new molecular biomarkers offer more accurate and earlier diagnosis of cardiotoxicity caused by chemotherapy as opposed to ancient tools. GDF-15 and microRNAs increased during the initial chemotherapy cycles, before cardiac dysfunction began to become symptomatic, implying that these two elements are responsive to hemodynamic cardiac stress.

These results are in line with previous research findings which showed that oxidative stress and mitochondrial dysfunction are precursors of structural damage that can be observed [5]. This was caused by GDF-15, an indicator of mitochondrial damage and oxidative burden, which had a positively, consistently, and significantly correlated association with exposure to drugs and functional alteration. On the same note, microRNAs, which regulate apoptosis and contractility of cardiomyocytes, report epigenetic reorganization to chemotoxic stress [12].

6.2 Biosensors are compared with their value.
The AUC of the new biomarkers (0.85-0.91 vs. 0.73-0.75) was also better than the traditional markers (troponin and BNP) hence their use as subclinical markers. Interestingly, the biomarkers were proved to be more diagnostic when combined with imaging parameters (GLS or MRI T1 mapping) [14].

Translational and Clinical Implications: This research has a number of implications to clinical and translational research and this includes the possibility to improve the assessment of cardiac and respiratory impairment in asthmatic patients.

6.3 Implications of Translational and Clinical

There are numerous implications of the current study on the clinical and translational research, including the potential to enhance the evaluation of cardiac and respiratory dysfunction in asthma patients.

The combination of these biomarkers and clinical practice will permit individual cardio-oncology. Both cardioprotective and personalized management of chemotherapy plans can be ensured by the timely identification of patients at the risk level and timely administration of dexrazoxane, ACE inhibitors, and beta-blockers [17]. Moreover, through the introduction of biomarker-based surveillance, the premature termination of treatment of low-risk patients could be reduced as much as possible, which will create an ideal balance between oncologic and cardiac safety.

CONCLUSION

This paper illuminates the need to enhance early detection of cardiotoxicity of chemotherapy as this is a more and more common problem in contemporary oncology. Though the treatment of cancer has greatly increased the survival rate of patients, the same therapy, particularly anthracyclines, cyclophosphamide and trastuzumab, has a dire effect on the heart. Conventional cardiac monitoring tools, echocardiography and standard biomarkers (troponin and BNP) are useful but lack sufficient sensitivity required to detect subclinical myocardial injury before the irreversible damages have taken place. To sum, the combination of the emergent cardiac biomarkers with imaging and computational modelling is an innovative move towards early diagnosis and treatment of chemotherapy-based cardiotoxicity. These innovations will enhance patient safety, maintain treatment effectiveness, and redefine the sphere of cardio-oncology as the sphere of personalized, preventative, and precision-based medicine, changing the approach to diagnosing the patient.

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