

## Early Subclinical Biomarkers in Onco-Cardiology to Prevent Cardiac Death

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### Abstract

Recent oncologic treatment has been associated with cardiovascular complications, such as hypertension, metabolic derangements, thrombosis, arrhythmia, and even cardiac death. Careful attention to detailed cardiac evaluation is required to optimize the anticancer treatment and prevent heart failure of patients undergoing chemoradiotherapy. Classical cardiovascular biomarkers like ANP, BNP, ProANP, NT-ProBNP, hsTnI, hsTnT, adropin, copeptin, and ET-1 are indicative of toxic effects in cancer patients with radiation, chemotherapy, and neoadjuvant treatment. Recently, miRNAs (i.e., miR-29, miR-146, miR-208, and miR-216) in the peripheral blood or exosome-derived miRNAs are attractive as novel biomarkers for drug-induced cardiotoxicity due to their highly conserved sequence and stability in body fluids. The anticancer treatment could lead to detectable increases of miRNAs in the absence of traditional cardiac biomarkers or cardiac remodeling. Circulating cardiovascular biomarkers provide earlier detection of cardiotoxicity from cancer treatments before irreversible damage occurs. An increased understanding of the potential roles and mechanisms may help to reveal the crosstalk between cancer therapy and cardiac issues.

**Keywords:** Biomarkers; Onco-cardiology; Cardiotoxicity

Onco-cardiology, also known as cardio-oncology, is an interdisciplinary subject in the field of cardiovascular care for cancer patients that have potential risk of developing heart disease due to certain oncologic drugs or radiation therapy (Table 1). Using a cloud-based health care database, Al-Kindi et al. [1] found that patients diagnosed with common cancers have an unexpectedly higher prevalence of Cardiovascular Disease (CVD) than general individuals. Overall, the prevalences were 33% for hematologic, 43% for lung, 17% for breast, 26% for colon, 35% for renal, and 26% for head and neck cancers.

The most common form of adverse effects is cardiomyopathy in regard to the use of anthracyclines as chemotherapeutic drugs. Compared with traditional chemotherapy, targeted cancer therapy is a novel strategy that has fewer cardiac complications on normal cells by inhibiting key molecules in signaling pathways involved in carcinogenesis and metastasis. However, either traditional or targeted chemotherapy can weaken the heart function or can even cause cardiac systolic dysfunction, cardiac ischemia, arrhythmias, pericarditis, and chemotherapy-induced repolarization abnormalities [2], underlined by deregulation of key signaling pathways in carcinogenesis (AMPK [3], RTKs-PDGFRs [4], etc.). Radiation-induced heart diseases (i.e., coronary artery disease, fibrotic changes to the valves, pericardium, and myocardium) have also been reported as the most common complications of cancer treatment strategies, especially in patients following radiation to the chest. The concurrent use of radiation and chemotherapy might have an increased risk of CVD in breast cancer [5,6]. Cancer patients with past cardiac history are usually more susceptible to the toxic effects of antineoplastic therapy and therefore are required to undergo realtime cardiovascular monitoring. For those without prior cardiovascular events, clinical oncologists may be more focused on diagnosis and treatment of neoplastic disease, rather than accessing side effects on the heart and vasculature.

Routine evaluation of cardiac function, even in asymptomatic individuals, is important as there is evidence that in patients developed Congestive Heart Failure (CHF) or asymptomatic decrease in Left Ventricular Ejection Fraction (LVEF) below 40%, the discontinuation of long-term trastuzumab-based therapy leads to reversible improvement

in cardiac function [7]. Assessment of drug-therapy-induced cardiotoxicity by conventional cardiovascular biomarkers (ANP, BNP, ProANP, NT-ProBNP, hsTnI, hsTnT, adropin, copeptin, and ET-1), circulating miRNAs (i.e., miR-29, miR-146, miR-208, and miR-216), or exosome-derived miRNAs might be considered in patients undergoing chemotherapy with cardiotoxic agents such as anthracyclines.

### Traditional Biomarkers for Cancer-therapy-related Cardiotoxicity

ANP and BNP are secreted by the atria and ventricles in response to pressure overload when heart failure develops, respectively [8]. In addition to maintain excretion and salt/water balance, they promote diuresis, natriuresis, vasodilatation and repress the Renin-Angiotensin-Aldosterone System (RAAS) [9,10]. Several studies have demonstrated that blood ANP and BNP levels are increased in patients with CVD [11,12]. Serum BNP levels are also shown to be elevated in cancer patients with the potential of CVD, suggesting that higher BNP may be indicative of progressive cardiotoxicity, especially with Anthracycline-Induced Cardiotoxicity (AIC) [13]. Feola et al. [14] found that the toxic effects following chemotherapy in breast cancer patients could be observed with plasma markers, the prospective study evaluated 53 patients with early breast cancer and candidate to adjuvant chemotherapy, in which blood BNP showed a positive trend of correlation with T3 LVEF.

Compared with ANP and BNP, their precursors ProANP and NT-proBNP are more sensitive for evaluating early cardiac impairment. Plasma levels of proANP and NT-proBNP are inversely correlated

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No.	Cancer	Treatment	Target	Complication	Dose-dependent	Ref
1	Breast cancer	Anthracycline (doxorubicin/ adriamycin, epirubicin)	Inhibition of DNA polymerases & DNA fragmentation	Arrhythmias, cardiac dysfunction, congestive heart failure	Doxorubicin: 200-250 mg/m <sup>2</sup> ; Epirubicin: 500 mg/m <sup>2</sup>	[57,58]
2	Leukemia	Mitoxantrone	The anthracenedione derivate	Cardiac systolic dysfunction	40 mg/m <sup>2</sup>	[59,60]
3	Hematologic neoplasms	Cyclophosphamide/ cytarabine, cytoxan	Alkylating agent	Cardiac systolic dysfunction, pericarditis, cardiomyopathy	Cyclophosphamide: 180 mg/kg >4 days	[61]
4	Gastrointestinal stromal tumor, Chronic myeloid leukemia, Renal cell carcinoma	Tyrosine kinase inhibitors (imatinib, radotinib, dasatinib, sunitinib, sorafenib, lapatinib, erlotinib, nilotinib, crizotinib)	Inhibition of hepatic drug metabolism	Cardiac systolic dysfunction, arrhythmias, heart failure, thrombophilia, pleural effusion	Imatinib: 400 mg/day; Radotinib: 730 mg/day; Dasatinib: 180 mg/day;	[62-68]
5	Solid tumors, Hematologic neoplasms	Interferon	Inhibition of cancer growing & multiplying	Cardiac systolic dysfunction, cardiomyopathy	Dose-independent	[69]
6	Breast cancer	Bevacizumab/avastin	Inhibitor of vascular endothelial growth factor	Cardiac systolic dysfunction, hypertension, thrombosis, cardiomyopathy, heart failure	15 mg/kg	[70]
7	Neuroendocrine, Lung, Prostate, Cervix, Pancreatic, Hepatic, Bladder, Biliary tumors	Capecitabine, 5-fluorouracil, gemcitabine	Antimetabolites	Cardiac ischemia, coronary vascular endothelial dysfunction and coronary thrombosis	Capecitabine: 1000-2500 mg/m <sup>2</sup> /day	[71-73]
8	Breast cancer	Taxanes (paclitaxel, docetaxel)	Antimicrotubule agents	Acute myocardial infarction, hypertension, deep vein thrombosis	Paclitaxel: 200 mg/m <sup>2</sup>	[74,75]
9	Breast cancer	Everolimus	mTOR inhibitor	Angina, hypertension, deep vein thrombosis	5-10 mg	[76]
10	Multiple myeloma	Bortezomib, carfilzomib	Proteasome inhibitor	Angina, hypertension, heart failure	Bortezomib: 1.3 mg/m <sup>2</sup> (4 days);	[77,78]
11	Ovarian germ cell tumor, Hodgkin's disease	Bleomycin, etoposide, cisplatin	Platinum-based regimen	Hypotension, pericarditis, acute substernal chest pain, coronary artery disease, myocardial ischemia, myocardial infarction, cerebral vascular accident, Raynaud's phenomenon	Bleomycin: 5 mg/m <sup>2</sup> (3 days)	[79,80]
12	Ovarian, Oesophageal, Small-cell lung cancer, Melanoma.	Combretastatin	Vascular disrupting agents	Acute myocardial infarction, hypertension, angina	36-54 mg/m <sup>2</sup>	[81]
13	Non-Hodgkin lymphoma	Vinblastine, vincristine, vinorelbine	Vinca alkaloids	Myocardial ischemia, vaso-occlusive complications, myocardial infarction	Vinblastine: 1.4 mg/m <sup>2</sup>	[82,83]
14	Breast, Colorectal, Non-small-cell lung, Glioblastoma, Renal cell, Ovarian, Cervical cancer	Trastuzumab/herceptin, bevacizumab, rituximab	Monoclonal antibodies	Cardiac ischemia, cardiac systolic dysfunction, cardiomyopathy, heart failure	Trastuzumab: Dose-independent; bevacizumab: 10 mg/kg; Rituximab: 375 mg/m <sup>2</sup>	[84-87]
15	Hodgkin's disease	Radiotherapy	Fibrous thickening of the pericardium	Pericarditis, pericardial effusion, cardiac tamponade	30-42 Gy: 2-fold increase in the risk of heart diseases	[88]

**Table 1:** Cardiovascular issues in cancer patients following chemoradiotherapy.

with LVEF and the degree of increase in their concentrations correlates with the severity of cardiotoxic effects [15,16]. In a prospective study involved 40 patients with breast cancer, ProANP and NT-proBNP levels might be used as reliable and sensitive markers in predicting early cardiac impairment caused by epirubicin-based chemotherapy [17]. Another retrospective study was conducted on 52 patients treated with High-Dose Chemotherapy (HDC) for aggressive malignancy, consisting of breast cancer, lymphoma, myeloma, sarcoma, uterine cancer, small cell lung cancer, and acute myeloid leukemia. Their results demonstrated that persistently increased plasma NT-proBNP after HDC administration is strongly associated with development of subsequent cardiac dysfunction, which was important for identifying patients at risk of developing chemotherapy-induced cardiotoxicity [18].

Troponin is a complex of three contractile regulatory proteins, troponin C, T and I, which plays critical role in muscle contraction. Among them, Troponins T and I are only found in cardiac muscle, and they will spill into bloodstream and perform as diagnostic biomarkers, especially for acute coronary syndrome because of cardiac muscle injury [19]. Compared with troponins I, the T type has a larger molecular weight and a longer half-life in blood, and the latter one is more affected by renal dysfunction than troponin I [20-22]. According to the results of Kilickap et al. [23], elevated serum levels of cardiac troponin-T (cTnT) could be detected in early stages of patients treated with anthracycline, which is related to diastolic dysfunction of the left ventricle.

Beyond traditional detection of troponin T and I, a high sensitive troponin assay is applicable to detect low abundance of circulating troponin in subclinical cardiovascular disorders [24]. In a prospective cohort of 19 women receiving anthracyclines and trastuzumab for HER2-positive breast cancer, the hsTnT level at 6 months was significantly higher in group R (LVEF reduction  $\geq$  5%) than in group N (LVEF reduction  $<$  5%). The elevated hsTnT showed a possible ability to predict a subsequent reduction of LVEF, indicating trastuzumab-induced cardiotoxicity [25]. Other researchers described that plasma concentration of hsTnI correlates with the risk of trastuzumab-induced cardiotoxicity [26-28]. Omland et al. [29] discussed the differences between the roles of troponin T and I in the prediction of cardiotoxicity in patients with stable coronary artery disease. They found that hsTnI correlated moderately with hsTnT ( $r=0.44$ ). Along with other parameters, the measurement of cardiac biomarkers such as NT-proBNP, hsTnT or hsTnI has been suggested to reflect and help monitor cardiac function during chemoradiotherapy [30,31].

Adropin is a recently identified peptide hormone that has been implicated in the regulation of cardiovascular regulation, energy homeostasis, and insulin resistance [32,33]. Aydin et al. [34] found that adropin was significantly increased in the endocardium, myocardium and serum in rats with Doxorubicin (DOX) treatment, which is a chemotherapeutic drug commonly used against various tumors [35]. In another study, also led by Aydin, suggested that the gradual increase in serum adropin could serve as an alternative to TnI for diagnosing Myocardial Infarction (MI) [36]. The cardiac failure associated with DOX-induced mitochondrial cardiomyopathy is the interference with oxidative phosphorylation and inhibition of ATP synthesis, which is related to adropin-energy metabolism and mitochondrial genome amplification [37,38]. Energy expenditure is mediated by adropin synthesized in the endocardium, myocardium, and epicardium [39]. Therefore, the upregulation of adropin after DOX exposure might indicate response of the cardiac endocardium and myocardium.

Copeptin is a 39-amino acid peptide hormone that is involved in cardiovascular regulation and fluid homeostasis [40]. As the C-terminal part of pro-arginine vasopressin, the concentration of copeptin has been shown to increase early on acute cardiac events such as Acute Myocardial Infarction (AMI). There are several lines of evidence that combined testing of copeptin and troponin at presentation is a promising strategy in patients with suspected Acute Coronary Syndrome (ACS) and therefore aids in early and safe rule-out of MI [41-43]. Moreover, elevated copeptin levels were correlated with worse prognosis and higher risk of adverse effects after AMI, especially in patients who develop heart failure [44].

The Endothelin (ET) family consists of three structurally related peptides, including ET-1, ET-2, and ET-3, each containing 21 amino acids. ET-1 is a kind of vasoconstricting hormone that play critical role in cardiovascular homeostasis [45]. The plasma ET-1 rose progressively during DOX treatment of patients with breast cancer who subsequently developed Congestive Heart Failure (CHF) [46]. Elevated plasma ET concentrations in patients with CHF would be a predictor of cardiac death [47].

## Circulating miRNAs Shedding More Light on Onco-cardiology

miRNAs are small, non-coding molecules, usually 22-24 nucleotides, that functions in translational repression and gene silencing. The expression levels of miRNAs in the peripheral blood are attractive as biomarkers of cardiotoxicity to chemoradiotherapy. As an ideal biomarker, the miRNA sequences are highly conserved among different species and are stable in human body fluids, such as plasma and serum, urine, saliva, amniotic fluid, and pleural fluid [48]. In addition, the miRNA levels can be easily detected in the laboratory by quantitative PCR and next-generation sequencing.

Several previous reports have demonstrated the great potential of miRNAs as clinical biomarkers for CVD [49,50]. Moreover, the cardio toxic effects on miRNAs expression in cancer patients were identified in few studies. Dinh et al. [51] reported that miR-29a decreased in circulation was associated with fibrosis of human heart with thoracic radiation therapy in patients with locally advanced non-small cell lung cancer. As an early biomarker of cardio adverse effects, circulating miR-29a may provide a new way to predict symptomatic toxicities, thereby enabling dose adjustment before onset of eventual heart failure.

Holmgren et al. [52] evaluated the early and late effects of DOX administration on the microRNAs expression profile, including miR-34a, miR-34b, miR-187, miR-199a, miR-199b, miR-146a, miR-15b, miR-130a, miR-214, and miR-424. Several miRNAs with differentiated expression levels were identified by using pure cardiomyocyte cultures derived from human Embryonic Stem Cells (hESC), suggesting that miRNAs profiling may identify more promising markers in onco-cardiology.

An in vivo study using rat model showed that plasma miR-208 levels increased significantly after isoproterenol-induced myocardial injury, which correlated with the concentration of TnI [53]. In a DOX-induced cardiotoxicity, miR-146a was shown to be upregulated in neonatal rat cardiac myocytes by targeting NRG-1/ErbB signalling. Inhibition of both ErbB2 and ErbB4 may be one of the reasons why those patients who received anti-ErbB2 antibody trastuzumab in combination with DOX suffer from congestive heart failure [54]. Another in vivo assay conducted by Suzzi et al. pointed out that the chronic myocardial toxicity induced by DOX in rats was associated with the modulation of microRNAs. Among them, miR-216b, which

was significantly elevated before overt toxicity, has the potential of a genomic indicator of cardio events [55].

It has been reported that tumor-derived exosomes could transfer miRNAs to recipient cells, which mediates cancer progression and metastasis. Emanuelli et al. [56] found that miRNAs, together with other acid nucleic molecules, proteins, and lipids can be released from exosomes. The plasma concentrations of exosomes and their cardiac miRNAs were positively correlated with hsTnI, which indicated a potential role for exosomes as novel biomarkers of myocardial injury.

## Summary

Cardiac side effects of cancer therapy may vary from mild transient blood pressure to serious complications, including arrhythmias, myocarditis, pericarditis, MI, cardiac ischemia, cardiomyopathy, and CHF. Routine cardiac monitoring of cancer patients during radiation, chemotherapy, or neoadjuvant treatment is imperative for long-term prognosis and life quality of cancer survivors. Blood biomarkers provide non-invasive, practical and reliable methods to identify high risk of cancer patients in cardiac functions, especially asymptomatic events.

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