Review Article

Drug Safety Issues in Cardio-oncology Practice

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Background : Patients suffering from cancer and heart disease are palliated by cardio-oncologist. The field cardio-oncology is a multi-disciplinary approach between cardiologists and oncologists. Recovery rates of cancer patients have increased over the past few years due to advent of potential drugs and targeted therapies. Combination of new targeted therapies with older chemotherapeutic regimens like anthracyclines are considered to be cardio-toxic.

Methods : This study aims to analyze published studies and guidelines to provide a systematic review of cardio-toxicity associated with chemotherapy and targeted therapy and its management.

Results : We present the algorithm of cardiovascular risk assessment to be done in cancer patients who are on cardio-toxic anticancer drugs.

Conclusion : Cardiovascular risk assessment in cancer survivors is critical because cardiovascular disease has become the leading cause of mortality among cancer survivors who have been exposed to cardio-toxic substances. The goal is to prevent, detect and manage cardio-toxicity in patients undergoing chemotherapy and targeted therapy by assessing cardiovascular risk prior to starting therapy, optimizing modifiable risk variables, and providing surveillance and treatment for an early sign of cardio-toxicity. Interdisciplinary approach between cardiologists and oncologists will certainly reduce vascular toxicity and thereby managing long term adverse effects.

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Key words **: Cardiology, oncology, drug safety, medication safety**

Cardio-oncology aims to minimize toxins in heart muscle cells, reduce illness and death counts by continuously enhancing the standard of living in patients suffering from cancer disease. Cardio-oncology is a recently evolved field in cardiology which comprises oncology study to treat patients. The introduction of new, more potent and focused medicines has resulted in steady increase in cancer survival rates. Among the modern therapies used along with few older chemotherapeutic regimens such as anthracyclines, being cardio toxic in nature. The first example of cardio-toxicity from cancer treatment was reported in relation to anthracyclines chemotherapy more than 50 years agoin the beginning of 1970[1]. Considering then, an expanded consciousness connection has been found between poor outcome and survival rate. Cardio-toxicity may be the price of cancer eradication. The fundamental goal of this integrated field of oncology and cardiology is to cure and prevent circulatory issues in cancer patients caused by anticancer drugs. There has been an exponential growth in survival rates due to new advancements in targeted therapies. With the help of research, it is very important to maintain an equilibrium between oncologic efficiency and cardio-toxicity. Most detrimental adverse effects of anticancer therapy are cardio-toxicity. Following anticancer drugs has measured percentage of cardio-toxicity, Doxorubicin has 3-26%, trastuzumab has 2-28% and sunitinib has 2.7-11%. Breast tumours and hematological malignancies have the highest rates of cardio-toxicity. Nearly about 17-23% of this harmful effect is noticed among patients having pediatric hematological cancer[2]. In a recent study, it was reported 6.6% of patients suffering from breast and hematological cancer further developed heart failure after receiving chemotherapy[3]. The fatal effects are not limited to cardio-toxicity or heart failure but also

Editor's Comment :

- Cardio-oncology is an interdisciplinary approach between cardiologists and oncologists in the treatment of patients with cancer and heart disease.
- Cardiovascular risk assessment among cancer survivors is important because cardiovascular disease becomes the most common cause of death among cancer survivors treated with cardiotoxic agents.
- A Multidisciplinary approach between cardiologist and oncologist will minimize vascular toxicity and manage long-term adverse effects.

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includes diseases associated with arteries of heart, heart rhythms irregularity, thromboembolism[4]. Illness like cancer and problems in arteries of heart share known pathways at molecular and cellular level. The main goal of this new integrated oncology and cardiology specialty is to treat and prevent circulatory issues in cancer patients as a result of these anticancer medicines.

This review aims to elaborate on cardio-toxicities related to chemotherapy and targeted therapy.

What is Cardio Oncology?

It is a multidisciplinary specialty of medicine that studies the molecular and clinical changes in the cardiovascular (CV) system caused by various cancer treatments (chemotherapy, targeted therapy, immunotherapy and radiotherapy).

Baseline risk factors for cardio-toxicity :

A. Advanced age, hypertension, and diabetes are examples of demographic risk factors and comorbidities.

B. Smoking, drinking, and obesity are all risk factors associated with our lifestyle.

C. Previous CV disease history, such as heart failure and sudden myocardial infarction.

D. Previous treatment history, such as the use of cardio- toxic medications or radiation.

Risk factors can be broadly classified into patients-related and therapy-related. The already established risk aspects for problems in arteries of heart like coronary artery disease (CAD), old age, high blood pressure, increased blood sugar level, tobacco smoking and postmenopausal status, are among the patient-related risk factors[5]. At lower anthracycline doses, genetic polymorphisms may contribute to an increased risk of cardiomyopathy, meaning that differences in an individual's DNA pattern could be very helpful to predetermine risks associated with heart. Patients of these kind may respond to anthracyclines irrespective of the dose administered[6]. Patients suffering from cancer may show higher margins of heart peptides such as high-sensitive troponin T (hsTnT) and N-terminal pro-BNP at the start of their treatment (NT-proBNP)[7]. Elevations of these peptides were highly connected to all-cause mortality, implying that disease development is linked to subclinical myocardial injury. Increased amount of chemotherapy dose whether coupled with different cancer therapies, previous to anthracycline use, cardiotoxicity mediastinal radiation, and the use of specific agents linked to an elevated case of heart muscle damage due to use of anthracyclines, trastuzumab and cyclophosphamide, are all therapy-related risk factors[8].

Pathomechanisms of cardiotoxicity with anticancer drugs

a. Apoptosis of cardiomyocytes.

b.Calcium ion channel alterations in cardiomyocytes.

c. Endothelial damage

Topoisomerase 2B aids doxorubicin in building a complex with DNA, resulting in the generation of reactive oxygen species that break down dsDNA strands, affecting calcium ion channel functioning in cardiomyocytes and eventually leading to mitochondrial failure.

This raises the question of whether the absence of Topo 2B can protect individuals from cardio-toxicity caused by Doxorubicin.

Trastuzumab, on the other hand, binds to HER2 with a high affinity, preventing it from dimerizing with other HER receptors. Cardiomyocytes are unable to activate the cell survival pathways associated with high ROS when HER2 signaling is blocked. As a result, blocking HER2 allows for the accumulation of reactive oxygen species (ROS) within cardiomyocytes, which leads to cardiac dysfunction linked with cellular apoptosis. Furthermore, with antibody-dependent cellular cytotoxicity, trastuzumab is able to recruit immune cells to tumour areas that overexpress HER2.

Chemotherapy Related Cardiac Dysfunction (CTRCD)?[8]

According to the European Society of Cardiology (ESC), CTRCD is defined as a decline in Left Ventricular Ejection Fraction (LVEF) >/5% in symptomatic patients or a drop in LVEF >/ 10% to an LVEF /< 50% in asymptomatic individuals.

Types of CTRCD?

After the introduction of trastuzumab for breast cancer in 1998, CTRCD classifications were created. As the drug's use grew[9], so did the number of documented cardio-toxic episodes, which were previously thought to happen equivalent in medical scenario as anthracyclines heart toxicity. Furthermore, it was described as two separate units, anthracyclines as Type 1 connected with heart toxicity and on the other hand Type 2 cardio-toxicity for trastuzumab[10]. These are pathophysiologic derived explanations, however there is no evidence with clinical implication for permanent cardiac dysfunction seen either of the types.It's also worth noting that treatment involving chemotherapy and chemotherapeutic drugs have a passive impression on cardiac muscle cells by interfering with body's circulatory system causing high blood pressure, arteries wall damage and irregular heartbeat.

Due to the cumulative prescribed dose, type 1 cardio-toxicity causes irreparable cardiac damage. The formation of reactive oxygen species, the buildup of anthracycline metabolites that impair sarcomere shape and function, and mitochondrial biogenesis have all been hypothesized as causes for their dose-dependent cardiac failure[11]. Anthracyclines are thought to have a higher risk of long-term heart impairment.

Trastuzumab is the best example of type 2 cardio-toxicity, which is defined by dose-independent reversible cardiac injury. Trastuzumab is a drug that has the binding capacity with a receptor called human epidermal growth factor receptor 2 and also hinder downregulated signaling processes and cellular functions. It is used to treat breast cancer.

There are two different types of CTRCD causing myocardial dysfunction and heart failure as illustrated in Fig 1.

Types of anthracycline related cardio-toxicities (Type 1 CTRCD) ?

A. Acute onset: This is a less common complication of post chemotherapy, and it usually manifests as LV systolic failure (may be reversible).

B. Early onset: Within a year of finishing anthracycline treatment, this becomes chronic and progressive (reversibility is debatable).

C. Late onset: This is a chronic, progressive condition that develops more than a year after treatment is finished. It is permanent and can take up to two decades to manifest.

Patients at higher risk of anthracycline induced cardio-toxicities?

Cancer patients who have already received high dose or has been administered anthracyclines (epirubicin 600mg/m^2 doxorubicin 450mg/m^2) or any patients diagnosed with LVEF 50% and having >/ 2 existing cardio vascular risk parameters are at greater risk of cardio-toxicity[12]. Even low dosages (300 mg/m^2) are associated with a significant risk of cardio-toxicity 1.6%[13]. Liposomal anthracyclines, such as pegylated liposomal doxorubicin, are much less cardio-toxic than traditional anthracyclines and have better efficacy, making them a suitable alternative for patients at high risk of cardio-toxicity.

Agent	Incidence(%)	Agent	Incidence(%)
Doxorubicin	2-48	Pertuzumab	<1.5
Epirubicin	1-3.3	Lapatinib	<1
LiposomalA	2	Sunitinib	2.7-19
Cyclophosphamide	7-28	Sorafenib	4-8
Ifosfamide	17	Pazopanib	7-11
Docetaxel	2-13	Imatinib	<3
Paclitaxel	<1	Everolimus	<1
Bevacizumab	1.6-4	Temsirolimus	<1
Trastuzumab	1.7-20		

Fig 1 — the two types of CTRCD

Type 2 CTRCD with anti Her2 agents?

Human epidermal growth factor receptor 2-targeted medicines are the gold standard approach of diagnosis for HER2 expressed breast cancer considering primary and secondary tumors[14]. Described by the upregulated expression of the HER2 gene in malignant cells, in both early and metastatic stages. Myocytes express the human epidermal growth factor receptor 2, which may protect against cardiac stress[15]. As a result, the proposed mechanism of cardio-toxicity involves HER2-targeted drugs binding to this cardioprotective pathway being disrupted.

Trastuzumab is the most frequently used anti-Her2 drug, which causes cardio-toxicity by raising oxidative stress and activating proteases via calcium ion channel channels via the EGFR downstream signaling pathway. This concludes in dilated cardiomyopathy and if amalgamate with anthracycline the risk is even higher[14]. Trastuzumab cardio-toxicity is not dose dependent (random effect) and appears to be extremely reversible as well[16]. The announced data rate of CTRCD without concomitant anthracycline use is nearly 3% and the same threat rises up to 5% when anthracycline is administered before trastuzumab. A study conducted by de Azambuja et al after 12 months of completion of truastuzumab therapy found that 74.5% patients had a chance of recovery any cardiac issues while only 20.5% patients did not have recovery, and it took 6.6 months as a median recovery time.

Interestingly, remedy with these medicinesmay be reinitiated if LVEF numbers returns to baseline or to acceptable values.

Toxicities and Indirect Cardiovascular Effects Associated with Cancer Therapies :

1.Vascular toxicity: therapy based on platinum, use of 5-FU (spasm), radiation (CAD), capecitabine, use of immunomodulator drugs that treat cancer and pathways associated with it.

2. Ventricular abnormalities: inhibitors that slow down cell proliferations and hinder receptor functions like HER2 and proteasome, TKI's, drug like anthracyclines and immune therapy for upregulating or downregulating immune cells.

3. Arrhythmias: therapy based involving platinum, inhibitors for ALK, ibrutinib, irregular heartbeats and diterpenes.

4.Hypertension: inhibitors that hamper functions of proteasome, therapy based on platinum, vascular

endothelial growth factor and ibrutinib.

5. Takotsubo's cardiomyopathy: 5-FU

6. Myocarditis: TKIs/ICPis

Diagnostic tests of CTRCD :

Prior to receiving potentially cardio-toxic chemotherapy, a baseline work-up should be performed, which includes a previous clinical information's, undergoing medical scrutiny, molecular testing, few procedures like echocardiography and an electrocardiogram. Predictive and descriptive models can be used to intervene the risk of cardio-toxicity in the accordance of the patient's attribute. A history of structural cardiac abnormalities, presence of risk in arteries either prior or future vulnerability to heart toxins treatments and advanced age are all factors that may predispose to cardiac adverse events.

Treatment :

A. The most extensively used technique is echocardiography because of its expanded availability, reproducibility, and lack of radiation exposure though this technique is very much operator dependent. When compared to Simpson's approach, which showed a 10% variation in LVEF calculation, 3D echo is substantially better than 2D echo and has demonstrated to be more accurate with a 5% inaccuracy[17]. In a 2016 study, 3D echocardiography was found to be similar to cardiac magnetic resonance imaging (MRI) in recognizing low clinical detection of less cardiac output. Advance study has demonstrated that it is possible to detect very minimum changes in cardiac functions.

Left ventricular longitudinal global strain (GLS) can be measured using speckle tracking echo, which is the longitudinal shortening in relation to baseline length (normal 18%, pathological 16%, grey zone) (16-18 %). When it comes to diagnosing chemotherapy-related heart failure, GLS outperforms LVEF testing.

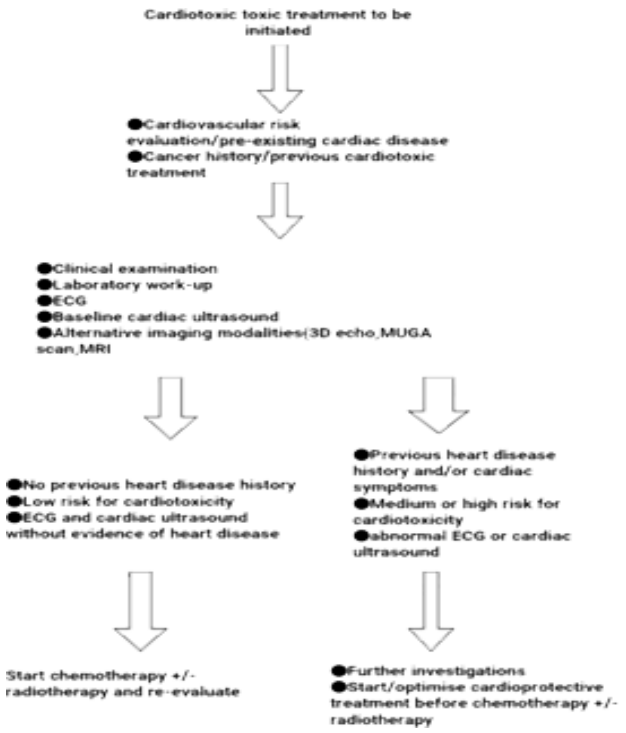
B. In the past, MUGA scan had good availability and high reliability, in patients with cancer disease multiple gated acquisition scan (MUGA) was used for diagnosing heart performance[18,19]. The main worry about this scan is its vulnerability to radiations. Patients undergoing regular treatment like MUGA scan prior to trastuzumab treatment in every three months as followed by Dutch Guidelines for breast cancer which states the amount of total radiation dose [20]. Sadly, MUGA can only come up with LVEF, which is insufficient for early CTRCD identification.

C. Cardiac MRI, it stands for cardiac magnetic resonance imaging (CMR) which is the gold standard to estimate overall cardiac function. Cardiac MRI portrays few advantages which incorporates absence of ionizing radiation, showing proper 3D space view, understanding LV/RV functions and also provide excellent discrimination of the endocardial/epicardial borders[21]. In individuals with anthracycline-induced cardiomyopathy, the unrelated predictor of significant unfavorable cardiac happenings is LV mass index[22]. It is extremely precise and repeatable, and the degree of late gadolinium enhancement can help identify patients with a poor prognosis, whereas diffuse fibrosis in T1 mapping can help predict late anthracycline cardio-toxicity.

D. Molecular biomarkers of heart such as Troponin, pro-BNP are used to predict any incoming cardiac problems. Troponin and brain natriuretic peptides have shown promising outcome in detecting subclinical cardio-toxicity during cancer treatment. They have the ability to forecast patients who are at risk of developing cardio-toxicity before to the start of cancer therapy, in addition to identifying late problems among cancer survivors. However, there are discrepancies in the statistics due to different study designs.To inform optimal clinical practice, more research with well conducted prospective trials is required.

E. A noninvasive nuclear imaging technique for measuring cardiomyocyte apoptosis is the 18 F labelled tetrapeptide caspase PET-CT scan.

What are the different varieties of Chemotherapy Related Cardiac Disorders?



Atherosclerosis, irregular heartbeat, diseases linked with coronary arteries, systolic and diastolic abnormalities, and hypertensionare all linked to anti-cancer therapy.

The major cardiovascular unfavorable events of anticancer drugs are as follows:

1. Myocardial Dysfunction: When the following heart echocardiographic criteria are met, significant cardio- toxicity after chemotherapy is considered. Any drop in Left Ventricular Ejection Fraction (LVEF) >/ 5% in symptomatic patients or drop in LVEF >/ 10% to an LVEF /< 50% in asymptomatic patients. Furthermore, global longitudinal strains (GLA) for left ventricular has been recommended as a biomarker of recently occurring cardio-toxicity due to certain percentage reduction in GLA during treatment like chemotherapy which is linked to a greater worse effect of substantial for left ventricular systolic abnormalities[12]. Chemotherapy-induced cardio-toxicity has been linked to two different pathophysiological pathways. The first is direct toxicity and killing of cardiac cells, which results in myocardial dysfunction that is permanent and probably irreversible (type I cardio-toxicity). The succeeding one is the suppression of cardiac cell's normal functions which follows a knock out in myocardium but changeable myocardial abnormalities. Duplet processes like these commonly interact with one another. Anthracycline cardio-toxicity is a classic example of type I cardio-toxicity, which is usually dose dependent[23]. Cardio-toxicity caused by trastuzumab is an example of type II cardio-toxicity that is not dose-dependent.

2. Coronary artery disease: Chance of accruing coronary atherosclerosis and acute coronary syndromes increases with the use of chemotherapeutic drugs like 5-fluorouracil and gemcitabine. Between the second and fifth days of treatment, continuous intravenous infusion of 5-fluorouracil can cause myocardial ischaemia, which presents as chest discomfort and ischemic ECG abnormalities. This happening is not dependent on dose[24]. Vasculitis, spasm, and thrombosis are the pathophysiological mechanisms involved. Bevacizumab and cisplatin are drugs that inhibits VEGF. They show linkage with reduced blood flow to the heart through endothelial defects, blood clots in arteries or veins[13]. Drug cisplatin is linked with cardiovascular disease is nearly about 2%[12]. Coronary artery disease also happens due to radiation therapy at the coronary ostia site, as well as an increased incidence of severe coronary syndromes. Succeeding vulnerability to Hodgkin lymphoma radiation, is substantial, even aftermany years later[25]. As a result, it's realistic to expect long-term follow-up and close monitoring after radiotherapy.

3. QT Prolongation: Arsenic trioxide, a highly successful treatment for recurrent acute promyelocytic leukaemia, can cause life-threatening torsades de pointes by prolonging the QT interval. Thus, in patients taking arsenic trioxide, the QT interval should be closely monitored and coexisting and precipitating variables such as electrolyte abnormalities, concurrent medicines, and other predisposing factors must be checked out before new individual cycle of therapy. Prolong QT interval might be due to inhibitors for proteasome and tyrosine kinase[26].

4. Arrhythmias: Irregular heart beat in both supraventricular and ventricular during chemotherapy are commonly noticed. Patients suffering from chronic lymphocytic and were undergoing treatment with ibrutinib developed AF[27]. Greater risk of developing bradyarrhythmias has been linked with the use of thalidomid. To avoid such happenings beta and calcium blockers are prescribed.

5. Systemic hypertension: Patients on VEGF inhibitors are more likely to develop systemic hypertension (11–45%). Risk of gaining hypertension or already having high blood pressure level gets elevated with the use of drugs like sunitinib and bevacizumab [28]. Sunitinib has also been connected to microcirculatory dysfunction due to its blockage of beta-type platelet-derived growth factor receptor. In these circumstances, inhibitors like angiotensin-converting-enzyme (ACE)and blockers like calcium channel pathway blockers are commonly administered[29].

6. Thrombotic diseases (arterial/venous): Cancer has been related to a prothrombotic environment, which can be aggravated by chemotherapy. Immuno-modulatory imide medicines including thalidomide, lenalidomide, and pomalidomide, which are routinely used to treat multiple myeloma, are linked to a 10 to 40% risk of thromboembolism. Variability has been associated to both patient and drug-related factors[30]. Anticoagulation with either low molecular weight heparin or warfarin is generally indicated for low-risk patients and prophylactic use of aspirin for highly vulnerable patients[31]. An increased risk of thrombotic events is connected with the use of bevacizumab, erlotinib, and cisplatin, but there is no specific thrombosis prevention advice.

What are the cardio-toxicities associated with newer molecules?

It was thought that with the introduction of novel

compounds such as targeted treatments or monoclonal antibodies, side effects such as cardio-toxicity would be significantly reduced. The introduction of targeted cancer medicines has greatly expanded the therapy options available to cancer patients. These medicines have resulted in the introduction of precision medicine into the clinic and improved patient outcomes by targeting specific signaling pathways hijacked by cancer cells[32]. In many cases, kinases and their downstream pathways that are hijacked by cancer cells are also important for normal cell vascular and metabolic homeostasis. Depending on the drug and the specific kinase target, inhibitors of these kinases may cause cardiovascular as a side effect. As an example, inhibition of the vascular endothelial growth factor (VEGF) signaling pathway end-up in hypertension, proteinuria, cardiomyopathy, and vascular disease in a subgroup of patients[33,34]. Therapeutics like Dasatinib, nilotinib, and ponatinib, new-generation ABL1 kinase inhibitors which are used for the treatment of CML, are connected with pulmonary hypertension (dasatinib), hyperglycemia and atherosclerosis (nilotinib), and hypertension and vascular disease (ponatinib). Arterial is-chemic events, such as MI, stroke, and limb ischemia, as well as venous thromboembolic (VTE) events, are the most significant vascular toxicities that could arise with the use of novel medicines. However, these substances can cause cardio-toxicities eg, Tyrosine kinase inhibitors (TKI) induced QT prolongation or even sudden death. Anti-Vascular Endothelial Growth Factor (VEGF) inspire hypertension, thromboembolism and even Immunotherapy induced myocarditis or pericarditis.

What is the medical treatment of CTRCD?

Patients with symptomatic heart failure or even asymptomatic cardiac dysfunction are advised Angiotensin Converting Enzyme Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) and beta blockers.

What is the cardio-protectants against anticancer drug related cardio-toxicities?

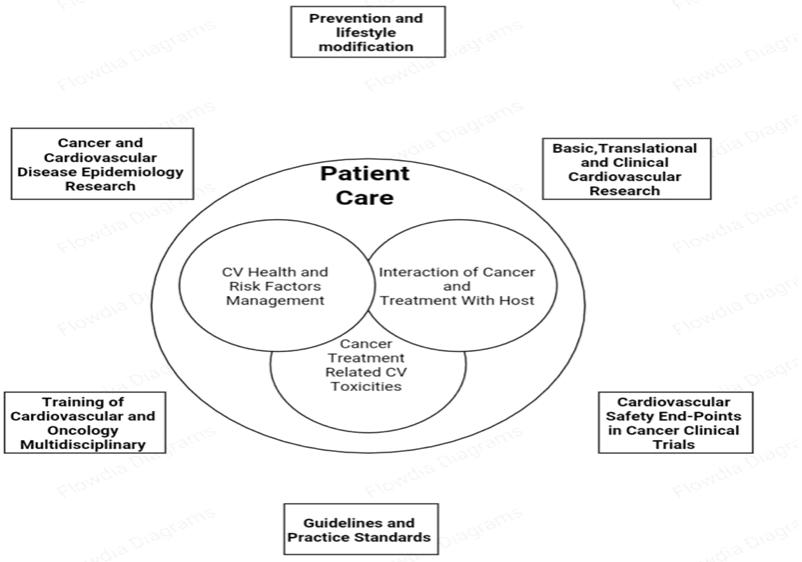
Cardio-protectants include ACEIs, ARBs, and beta blockers. Several experiments are being conducted to strategize the avoidance of cardio-toxicity caused by chemotherapies. The PRADA research looked at how Candesartan (ARB) reduced LVEF in patients receiving adjuvant anthracycline-based chemotherapy when compared to metoprolol or placebo. The role of carvedilol and enalapril in preventing left ventricular dysfunction in hematological malignancies was investigated in the OVERCOME research. Other cardio-protectants, such as statins, N-acetyl cysteine, Coenzyme Q 10, amifostine, and calcium channel blockers, have been explored, but there isn't enough evidence to recommend their use in ordinary clinical practice. STOP CA and prevent trials are two ongoing global trials evaluating the role of statins in reducing cardio-toxicity.

What are the vascular side effects of anticancer chemotherapies?

Previously followed treatment pattern cytotoxic chemotherapies and radiation therapy (RT) still remains in practice, despite of having targeted cancer medicines and immunotherapies. Vascular diseases include coronary artery disease (CAD) and peripheral vascular disease (PAD). Nolotiniband ponatinib are classified as tyrosine kinase inhibitors. They may promote undesirable incidents on peripheral arterial circulations and furthermore elevate the chances of acquiring PAD. Neck irradiation in the past has been linked to an increased risk of carotid artery atherosclerosis and ischemic stroke.

Type 1: Persistent risks of vascular events continue even after drug discontinuation e.g. Nilotinib.

Type 2: Risks of toxicity is only with ongoing drug therapy but it resolves after completion of treatment eg, 5 Flurouracil.



Components of Cardio-Oncology Service:

Active collaboration and partnership between cardio-vascular and cancer professionals is a key theme of the cardio-oncology service. From comprehensive National Cancer Institute–designated facilities and tertiary referral centers to community-based oncology centers, various models have been proposed, most reflecting distinctions in particular cancer programs[35,36]. Multidisciplinary collaboration involving medical and radiation oncologists, hematologists, surgeons, palliative care specialists, pharmacists, and cardiologists is a prevalent theme in these programs (including cardiovascular imaging, HF, interventional cardiology, electrophysiology, and more recently, vascular medicine subspecialties).

Future Research Directions in Cardio-Oncology:

CTRCD risk assessment, detection, and prevention are critical. The goal of cardio-oncology is to prevent, detect, and treat cardio-toxicity as early as possible. To determine the exact pathways involved in chemotherapy-induced cardio-toxicity, more research and study is needed.

1. Detailed monitoring of vascular and metabolic side effects during clinical trials and after drug approval in the general population.
2. Once a medicine is licensed, multi-institutional registries are used to identify vascular and metabolic side effects.
3. Pharmaceutical companies providing open-source data on cancer medicines' having cardiovascular side effects.
4. Biomarkers and imaging are used to do a comprehensive and systematic vascular phenotyping. Cardio-oncology personalized/precision medicine.
5. Identifying patients/individuals for having cardiovascular toxicities while undergoing cancer treatment.
6. Single integrated registry with researchers, patients, providers, and clinical diagnostic laboratories entering family history, clinical and research data, and accompanying bio-specimens (including DNA) in a deidentified manner.
7. Inquiries into genetics to see whether there's a danger of toxicity.
8. Improved vascular imaging and its application in the cardio-oncology population. In academic cardio-oncology, fundamental, translational, and clinical research initiatives are all integrated.
9. For preclinical testing of new drugs, more robust model cell systems (e.g., induced pluripotent stem cells) and animal models are being developed.
10. More research into the processes of shared risk factors (such as genetic risk factors) in cancer and cardiovascular disease.

Conclusion

MD Anderson Cancer Center's groundbreaking developments and hyper-drive in July 2000 grew into a complete cardiovascular discipline merged with oncology. This was a trial initiative to help cancer patients and survivors identify, manage, and prevent cardiovascular diseases. Cardio-oncology has grown naturally as a new field, and it is progressively becoming a part of everyday clinical practice. It necessitates the participation of numerous medical disciplines as well as a multidisciplinary approach in addition to oncologists and cardiologists.

References

1 Koutsoukis A, Ntalianis A, Repasos E, Kastritis E, Dimopoulos MA, Paraskevaidis I — Cardio-oncology: a focus on cardiotoxicity. *European Cardiology Review* 2018; **13(1):** 64.
2 Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ET — Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. *Journal of the American College of Cardiology* 2017; **70(20):** 2536-51.
3 Abdel Qadir H, Bobrowski D, Zhou L, Austin PC, Calvillo Argüelles O, *et al* — Thavendiranathan P. Statin Exposure and Risk of Heart Failure After Anthracycline or Trastuzumab Based Chemotherapy for Early Breast Cancer: A Propensity Score Matched Cohort Study. *Journal of the American Heart Association* 2021; **10(2):** e018393.
4 Perez IE, Taveras Alam S, Hernandez GA, Sancassani R — Cancer therapy-related cardiac dysfunction: an overview for the clinician. *Clinical Medicine Insights: Cardiology* 2019; **13:** 1179546819866445.
5 Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM — Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *Journal of the National Cancer Institute* 2010; **102(1):** 14-25.
6 Blanco JG, Sun CL, Landier W, Chen L, Esparza-Duran D, Leisenring W, *et al* — Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes—a report from the Children's Oncology Group. *Journal of Clinical Oncology* 2012; **30(13):** 1415.
7 Pavo N, Raderer M, Hülsmann M, Neuhold S, Adlbrecht C, Strunk G, *et al* — Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. *Heart* 2015; **101(23):** 1874-80.
8 Curigliano G, Mayer EL, Burstein HJ, Winer EP, Goldhirsch A — Cardiac toxicity from systemic cancer therapy: a comprehensive review. Progress in cardiovascular diseases. 2010; **53(2):** 94-104.
9 Campia U, Moslehi JJ, Amiri-Kordestani L, Barac A, Beckman JA, Chism DD, *et al* — Cardio-oncology: vascular and metabolic perspectives: a scientific statement from the American Heart Association. Circulation 2019; **139(13):** e579-602.
10 Ewer S, Lippman SM — Type II chemotherapy-related cardiac dysfunction: Time to recognize a new entity by Michael. *Journal of Clinical Oncology* 2005; **23:** 2900-2.
11 Teske AJ, Linschoten M, Kamphuis JA, Naaktgeboren WR,

Leiner T, van der Wall E, Kuball J, van Rhenen A, *et al* — Cardio-oncology: an overview on outpatient management and future developments. *Netherlands Heart Journal* 2018; **26(11):** 521-32.
12 Bair SM, Choueiri TK, Moslehi J — Cardiovascular complications associated with novel angiogenesis inhibitors: emerging evidence and evolving perspectives. *Trends in cardiovascular medicine* 2013; **23(4):** 104-13.
13 Di Lisi D, Manno G, Novo G — Subclinical Cardiotoxicity: The Emerging Role of Myocardial Work and Other Imaging Techniques. *Current Problems in Cardiology* 2021; **16:** 1008-18.
14 Shakir DK, Rasul KI — Chemotherapy induced cardiomyopathy: pathogenesis, monitoring and management. Journal of clinical medicine research 2009; **1(1):** 8.
15 Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, *et al* — ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). European heart journal. 2016 Sep 21;37(36):2768-801.
16. Tocchetti CG, Cadeddu C, Di Lisi D, Femmino S, Madonna R, Mele D, Monte I, Novo G, Penna C, Pepe A, Spallarossa P. From molecular mechanisms to clinical management of antineoplastic drug-induced cardiovascular toxicity: a translational overview. Antioxidants & redox signaling. 2019 Jun 20;30(18):2110-53.
17. Okwuosa TM, Akhter N, Williams KA, DeCara JM. Building a cardio-oncology program in a small-to medium-sized, nonprimary cancer center, academic hospital in the USA: challenges and pitfalls. *Future cardiology* 2015; **11(4):** 413-20.
18 Halazun JF, Wagner HR, Gaeta JF, Sinks LF — Daunorubicin cardiac toxicity in children with acute lymphocytic leukemia. *Cancer* 1974; **33(2):** 545-54.
19 Tan LL, Lyon AR — Role of biomarkers in prediction of cardiotoxicity during cancer treatment. *Current treatment options in cardiovascular medicine* 2018; **20(7):** 1-4.
20 Odak M, Kayani WT — MUGA Scan. StatPearls [Internet]. 2020.
21 Manolis AA, Manolis TA, Mikhailidis DP, Manolis AS — Cardiovascular safety of oncologic agents: a double-edged sword even in the era of targeted therapies–Part 2. *Expert opinion on drug safety* 2018; **17(9):** 893-915.
22 Neilan TG, Coelho-Filho OR, Pena-Herrera D, Shah RV, Jerosch-Herold M, Francis SA, *et al* — Left ventricular mass in patients with a cardiomyopathy after treatment with anthracyclines. *The American journal of cardiology* 2012; **110(11):** 1679-86.
23 Monsuez JJ, Charniot JC, Vignat N, Artigou JY — Cardiac side-effects of cancer chemotherapy. *International journal of cardiology* 2010; **144(1):** 3-15.
24 Semeraro GC, Lamantia G, Cipolla CM, Cardinale D — How to identify anthracycline-induced cardiotoxicity early and reduce its clinical impact in everyday practice. Kardiologia Polska *(Polish Heart Journal)* 2021; **79(2):** 114-22.
25 De Keulenaer GW, Doggen K, Lemmens K — The vulnerability of the heart as a pluricellular paracrine organ: lessons from unexpected triggers of heart failure in targeted ErbB2 anticancer therapy. Circulation research 2010; **106(1):** 35-46.
26 O'Hare M, Sharma A, Murphy K, Mookadam F, Lee H — Cardio-oncology Part I: chemotherapy and cardiovascular toxicity. *Expert review of cardiovascular therapy* 2015; **13(5):** 511-8.
27 Kim H, Chung WB, Im Cho K, Kim BJ, Seo JS, Park SM, *et al* — Diagnosis, treatment, and prevention of cardiovascular toxicity related to anti-cancer treatment in clinical practice: an opinion paper from the working group on cardio-oncology of the Korean Society of Echocardiography. *Journal of cardiovascular ultrasound* 2018; **26(1):** 1-25.
28 Porêba MA — Journal of Clinical Oncology and Cancer Therapy. *J Clin Oncol* 2020; Jul 29.
29 Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, *et al* — Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *The Lancet* 2007; **370(9604):** 2011-9.
30 Manolis AA, Manolis TA, Mikhailidis DP, Manolis AS — Cardiovascular safety of oncologic agents: A double-edged sword even in the era of targeted therapies–part 1. *Expert opinion on drug safety* 2018; **17(9):** 875-92.
31 Andersen MM, Ayala-Peacock D, Bowers J, Kooken BW, D'Agostino Jr RB, Jordan JH, *et al* — Effect at One Year of Adjuvant Trastuzumab for HER2+ Breast Cancer Combined with Radiation or an Anthracycline on Left Ventricular Ejection Fraction. *The American journal of cardiology* 2020; **25(12):** 1906-12.
32 Walls GM, Lyon AR, Harbinson MT, Hanna GG — Cardiotoxicity following cancer treatment. *The Ulster medical journal* 2017; **86(1):** 3.
33 Kushwah AS — Cardiotoxicity associated with chemotherapy: Need for treatment and prophylaxis role. *Heart failure* 2013; **11:** 13.
34 Molinaro M, Ameri P, Marone G, Petretta M, Abete P, Di Lisa F, *et al* — Recent advances on pathophysiology, diagnostic and therapeutic insights in cardiac dysfunction induced by antineoplastic drugs. *BioMed research international* 2015; 25: 2015.
35 Barac A, Murtagh G, Carver JR, Chen MH, Freeman AM, Herrmann J, *et al* — Cardiovascular health of patients with cancer and cancer survivors: a roadmap to the next level. *Journal of the American College of Cardiology* 2015; **65(25):** 2739-46.
36 Matos E, Zakotnik B, Kuhar CG — Effectiveness of adjuvant trastuzumab in daily clinical practice. *Radiology and oncology* 2014; **48(4):** 403.