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LITERATURE REVIEW ON DEVELOPING CARDIAC DISORDERS- A RISK DUE TO ANTICANCER DRUGS

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ABSTRACT

As in the current scenario advanced cancer treatment have contributed decreased cancer related mortality. But even then there are chances for cancer survivors to cardiovascular diseases. Unfortunately it is mostly due to the anticancer drugs especially due to anthracyclines, gemcitabine, cisplatin, alkylating-agents and kinase-inhibitors (KIs) such as ibrutinib. The major thing to discuss is patient may affected with hypertension, diabetes or heart failure which increase an individual's arrhythmia susceptibility. Combination treatments for cancers increased arrhythmia risk. It is very much important to reduce this risk through identification and prevention of this drug related problems. Future anticancer drug trials should consider all these things to minimize the mortality and morbidity relating these side effects.

KEYWORDS: Anticancer drugs, Cardiac rhythm disorders, Anthracyclines, Gemcitabine, Kinase inhibitors.

INTRODUCTION

Due to the current lifestyle and other genetic risk factors patients with both cancer and cardiovascular disease are increasing day by day. The anticancer agents like cytotoxic agents and targeted therapies used to treat cancer, including classic chemotherapeutic agents, monoclonal antibodies that target tyrosine kinase receptors, small molecule tyrosine kinase

inhibitors, and even antiangiogenic drugs and chemoprevention agents such as cyclooxygenase-2 inhibitors, all affect the cardiovascular system. One of the reasons is that many agents reach targets in the microenvironment and do not affect only the tumor. Combination therapy for cancer enhances the cardiotoxicity and radiotherapy. A patient with cancer or preneoplastic condition who is taking anticancer therapy or chemoprevention is now at a high risk of developing cardiovascular health.[1] Cardiovascular risk is a major factor that limit the effective therapy of cancer using major anticancer drugs.

Review of literature

Adriana Albini *et al* (2009) published a review on Cardiotoxicity of Anticancer Drugs: The Need for Cardio-Oncology and Cardio-Oncological Prevention summarized the potential cardiovascular toxicities for a range of cancer chemotherapeutic and chemo-preventive agents and emphasize the importance of evaluating cardiovascular risk when patients enter into trials and the need to develop guidelines that include collateral effects on the cardiovascular system.[1]

Nabeel Quryshi*et al* (2018) published a review on Chemotherapeutic-Induced Cardiovascular Dysfunction: Physiological Effects, Early Detection—The Role of Telomerase to Counteract Mitochondrial Defects and Oxidative Stress summarized the Chemotherapy can adversely affect cardiovascular physiology, resulting in the development of cardiomyopathy, heart failure and micro-vascular defects. Specifically, anthracyclines are known to cause an excessive buildup of free radical species and mitochondrial DNA damage (mtDNA) that can lead to oxidative stress-induced cardiovascular apoptosis.[2]

Carmela Coppola*et al* (2017) published a review on Management of QT prolongation induced by anti-cancer drugs: Target therapy and old agents. Different algorithms for different drugs summarized the Patients undergoing chemotherapy have a higher risk of developing cardiovascular complications, and the risk is even greater if there is a history of heart disease. Moreover, anthracyclines, together with a wide range of biological molecules, such as trastuzumab and ErbB2 inhibitors, are well known to have cardiotoxic effects.[3]

Joachim Alexandre*et al* (2018) published a review on Anticancer drug-induced cardiac rhythm disorders: Current knowledge and basic underlying mechanisms summarized the causal relationship of a particular anticancer drug with cardiac arrhythmia occurrence remains challenging due in part to patient comorbidities and complex treatment regimens.[4]

Michael G. Fradley *et al* (2015) published a review on QT Prolongation and Oncology Drug Development summarized the QT interval prolongation does not always translate into an increased clinical risk of arrhythmia, current guidelines may be too restrictive for novel oncology drugs.[5]

Cardiotoxicity – The real phase

The National Cancer Institute defines cardiotoxicity in very general terms as "toxicity that affects the heart". Now the clinical researchers are trying to solve the cardiac issues relating to the anticancer therapy. Some defined drug-associated cardiotoxicity as one or more of the following: 1) cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF), either global or more severe in the septum; 2) symptoms associated with heart failure (HF); 3) signs associated with HF, such as tachycardia, 4) reduction in LVEF from baseline that is in the range of less than or equal to 5% to less than 55% with accompanying signsor symptoms of HF, or a reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without accompanying signs or symptoms. This definition does not include subclinical cardiovascular damage that may occur early in response to some chemotherapeutic agents; thus, to date, an ideal definition is lacking. [1]

Cardiotoxicity can develop in the following ways

1. Subacute
2. Acute
3. Chronic manner

Acute or Sub acute cardiotoxicity is characterized by abnormalities in ventricular repolarization and electrocardiographic QT-interval changes, by supraventricular and ventricular arrhythmias, or by acute coronary syndromes and pericarditis and/or myocarditis-like syndromes, observed any time from the initiation of therapy up to 2 weeks after termination of treatment

Chronic cardiotoxicity

Chronic cardiotoxicity may be differentiated in two subtypes based on the onset of clinical symptoms. The first subtype occurs early, within 1 year after termination of chemotherapy, and the second occurs late, more than 1 year after chemotherapy. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction that leads to severe congestive cardiomyopathy and that may ultimately lead to death.[3]

Mechanism and effects of anti cancer therapy on cardiovascular system

Mechanism

Many drugs induce rapid apoptosis/necrosis, and a compromise of repair activity in proliferating cancer cells and the myocardium, which ultimately contributes to the increase of cardiotoxicity. Some also cause thrombosis and blood clot that increase the risk. Chemotherapy-derived injury may also lead to CVS toxicity. It also increase oxidative stress, radical formation and RNA destruction.

Oxidative stress involved in cardiotoxicity

High levels of endogenously produced ROS and chemotherapy-induced oxidative stress are damaging arterioles, capillaries, arterial capillaries etc. Antineoplastic agents induce oxidative stress. Oxidative stress is characterized by the imbalance in the production of reactive oxygen species and neutralizing antioxidants. Oxidation of Low-density Lipoprotein (LDL) within the endothelium is a predecessor for plaque generation. It increases CVS risk.[4] This oxidative stress stems from the increase of lipid peroxidation products that cause reduction of antioxidants (vitamin E, vitamin C, and beta-carotene) within plasma.

Free radical formation (Reactive Oxygen Species) during Cardiotoxicity

Cisplatin, generates free radicals. Through the interaction with DNA and the inhibition of thioltransferase, cisplatin generates free radicals and increase of oxidative stress.[6] These hydroxyl radicals are highly reactive and often induce the formation of toxic aldehyde 4-hydroxynenal through a reaction with membrane localized polyunsaturated fattyacids.[11]

Effects of anticancer therapy on the cardiovascular system

Direct effects on the heart

They directly damage the cardiomyocytes or cause inflammation of the pericardium. Anthracyclines, induce mitochondrial apoptosis pathways and free radical production. 5-Fluorouracil, a widely used chemotherapeutic, has direct toxic effects on vascular endothelium that involve endothelial nitricoxide. TKIs, for example, sorafenib and sunitinib, havebeenalso been associated with direct cardiotoxicity.[7]

Effects on the coagulation system

Increase in blood clotting in the vessels, which leads to thrombosis. Most of them are angiogenesis inhibitors.

Hypertension

Hypertension is a common adverse effect with bevacizumab, sorafenib, and sunitinib.

Treatment for cardiovascular system effects due to anticancer drugs

No guidelines have been developed specifically for the definition, detection, or therapy of cardiotoxicity from antineoplastic therapy, so it is imperative that these guidelines be defined. For the time being guidelines published by the American College of Cardiology and American Heart Association can be taken as one.[2]

Table 1; Guidelines published by the American College of Cardiology and American Heart Association.

Approach	Before antineoplastic therapy	During antineoplastic therapy and follow-up
Clinical assessment	Familial and personal anamnesis; physical examination; diagnosis; risk assessment	Physical examination; cancer therapy evaluation; risk reassessment
Tests	Blood pressure assessment; chest radiography; LVEF evaluation by any of these means: ECG, dynamic ECG, Eco-Doppler, MUGA scanning	Blood pressure assessment; chest radiography; LVEF follow-up by any of these means: ECG, dynamic ECG, Eco-Doppler, MUGA scanning
Serum markers	Troponin isoforms; B-type natriuretic peptide; myeloperoxidase	Troponin isoforms; B-type natriuretic peptide myeloperoxidase
Prevention-Treatment	Lifestyle adjustments; cardio protection; ACE inhibitors; angiotensin II receptor blockers; β-blockers; prevention of thromboembolism with aspirin or anticoagulants or platelet antiaggregants	ACE inhibitors; angiotensin II receptor blockers; β-blockers; cardiologic therapeutic regimen titration; other appropriate therapies (i.e., anticoagulant therapies); change of antineoplastic therapeutic regimen (drug, schedule, or suspension)

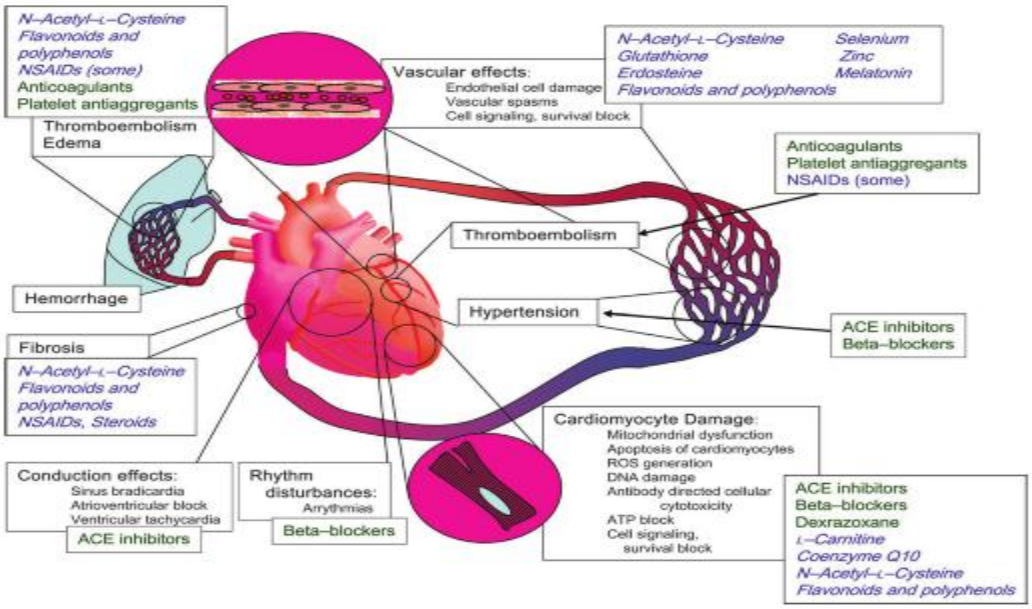

Fig. 1: Drugs that can be used to control CVS toxicity after anticancer treatments.

Established biomarkers

1. Troponin
2. Inflammatory Markers/C-Reactive Protein (CRP)
3. New Biomarkers: Telomere Length and Telomerase Activity

Risk factors relating to CVS diseases

Risk factors conventionally related to cardiovascular disease such as smoking, hypercholesterolemia, hypertension, obesity, diabetes mellitus, physical inactivity, psychosocial ailments and alcohol consumption have been related to shortened telomeres.

CONCLUSION

Even though as mentioned above some measures are there to minimize the risk of anticancer drug induced cardiac diseases most of them are still experimental in nature. All the aspects relating to CVS toxicity of anticancer drugs should be considered during dug development itself in Phase 1 part of clinical trial to minimize them. Identification of the development of toxicity is at most important as early as possible. In this developing stage the key goal should be the development of anticancer drug with minimum or without cardiac toxicity. In cancers with high probability of long-term survival, such as breast and prostate cancers, it is very important to consider cardiovascular risks.

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