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Cardiotoxicity associated with chemotherapy: Need for treatment and prophylaxis role

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ABSTRACT:

Cardiotoxicity is a well-known potential side effect of several chemotherapeutic agent. Patients undergoing chemotherapy highly exposed to cardiac complications. Chemotherapeutic agents like anthracycliines, cyclophosphamide and signaling inhibitors like human monoclonal antibodies and tyrosine kinase inhibitors worsen cardiovascular system. A number of cardiovascular events occur during cardiotoxicity phase like cardiomyopathy, thromboembolic disorders, hypertension and coronary artery spasm. Several procedures employed for early detection of cardiotoxicity either based on estimation of cardiac biomarkers or by cardiac imaging. Early assessment of preexisting medical condition in cancer patient reduces risk of cardiotoxicity. Cardioprotection achieved by limiting chemotherapy dose, use of antioxidant and iron chelating agents. Cardiologist and oncologist work together for successful management of cardiotoxicity Work is currently progressing for early prediction and management of cardiotoxicity developed during chemotherapy.

1. Introduction

During last few decades survival rate of cancer patient risen dramatically. Early detection and new treatment approaches enhance quality of life in cancer patients. In addition onset of cardiac complication in patients undergoing chemotherapeutic treatment affects the patient's life[1]. Cardiotoxicity develop mortality in patient survive from neoplastic disorders. The cancer survivor study revealed that there is increased risk of cardiovascular mortality up to 8 fold in cancer survivors as compared to healthy people after 25 years of therapy[2]. Early detection of cardiotoxicity reduces prevalence of morbidity in cancer patient. Various diagnostic techniques like endomyocardial biopsy elevation in troponin level predicts early cardiotoxicity[3]. The risk of development of cardiotoxicity in cancer patient often depends upon factors like dosing regimen, concomitant use of anthracyclines with other chemotherapeutic agents, age of patient, preexisting medical condition[4]. The aim of this review is to attempt to summarize cardiac events associated with chemotherapy, diagnostic prophylactic and treatment aspects of cardiotoxicity in cancer patients, targeted chemotherapy, the need for collaboration in between cardiologist and oncologists.

1.1Cardiotoxicity

National Cancer Institute defines Cardiotoxicity as 'toxicity that affects the heart' this definition limits the direct effect of drugs on the heart. Chemotherapeutic agents affect both vascular system and heart[5]. Cardiotoxicity comprise several cardiac complications like variation in blood pressure, electrophysiological changes in cardiac muscles, arrhythmias, pericarditis, myocarditis cardiomyopathy, left ventricular dysfunction or heart failure[6]. Cardiotoxicity induced by anthracyclines persist in acute, early-onset chronic progressive and late-onset chronic progressive. Clinical manifestation of acute cardiotoxicity characterized by sympto ms like transient arrhythmias or abnormal electrocardiographic ST/T and QT interval changes with acute cardiac decompensation and myocarditis-pericarditis syndrome. Symptoms generally appear during treatment and vanishes after discontinuation of therapy. Early-onset chronic progressive cardiotoxicity manifest as cardiomyocyte damage along with late signs of cardiotoxicity. Cardiotoxicity persist during therapy or occur at least one year of termination of chemotherapy. Late-onset chronic progressive cardiotoxicity manifest as cardiac stress due to lack of ability of cardiomyocytes to meet demand and less availability of cardiomyocytes for hypertrophic remodeling of the left ventricle.

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This type of cardiotoxicity appears any time after chemotherapy and is age dependent[7, 8].

1.2 Cardiotoxicity of chemotherapeutic agent

Chemotherapeutic agents injure cardiovascular system result in reversible or irreversible cardiotoxicity which leads to congestive heart failure (CHF). Cytostatic chemotherapeutic agent like anthracyclines considered to be cytotoxic cause irreversible cardiotoxicity by generating reactive oxygen Species (ROS), impairing intracellular calcium homeostasis and mitochondrial metabolism. Some Signaling inhibitors like human epi-dermal growth factor receptor 2 (HER2/erbB2) and angiogenesis inhibitors used in chemotherapy also associated with cardiotoxicity[9,10]. Chemotherapeutic agents with potential cardiotoxicity listed in tables: 1 & 2.

Table 1-Cytostatic chemotherapeutic agent associated cardiotoxicity

Drug/class	Cardiotoxicity at dose	Population studied	Mechanism of cardiotoxicity	Cardiac events	Reference
		Anthracyclines			
Doxorubicin	550 mg/m^2	Carcinoma Lymphosarcoma	Oxidative stress Iron chelation Impaired calcium homeostasis	Cardiac dysfunction, Congestive Heart failure	[11-13]
Idarubicin	Cumulative dose 150-290 mg/m^2	Acute Myeloid Leukemia	Sarcoplasmic reticulum function impaired Oxidative stress	Congestive heart failure	[14]
Epirubicin	Cumulative dose >950 mg/m^2	Metastatic Breast cancer	Oxidsative stress Vascular endothelial cell injury	Vascular pain, Congestive heart failure	[15, 16]
		Alkylating agent			
Cyclophosphamide	>1.55 mg/m^2/d for 4 consecutive days	Acute lymphoblastic leukemia Aplastic anaemia	Endothelial capillary damage Myocardial necrosis	Congestive Heart failure, Pericarditis	[17]
Ifosfamide	10-16 g/m^2	Hodgkin disease	Loss of striation Fragmentation of muscle fibre Myocardial depression	Congestive Heart failure	[18]
Mitomycin	> 30mg/m2	Breast cancer Prostate cancer Gastric cancer	Oxidative stress	Left ventricular dysfunction, Congestive heart failure	[19, 20]
Cisplatin	10 mg/kg i.p.	Albino rats	Oxidative stress	Arrhythmias, Myocarditis, Congestive heart failure	[21]
		Anthraquinone			
Mitoxantrone	Cumulative dose up to 140 mg/ m^2	Acute Myeloid leukemia Multiple sclerosis	Oxidative stress	Bradycardia, Congestive heart failure	[22,23]
		Antimetabolite			
5-fluorouracil	400 mg/ m^2 bolus	Adenocarcinoma	Coronary vasospasm	Angina, Myocardial infarction, Arrhythmias	[24]
Capecitabine	1500 mg/m^2 twice a day	Colon cancer	Coronary vasospasm	Myocardial infarction, Angina	[25]

Table 2- Signalling inhibitors associated cardiotoxicity

Class /Drug	*Molecular target*	Clinical indication	Mechanism of cardiotoxicity	Cardiac event	Reference
		Human mAb			
Trastuzumab	HER -2	Metastatic breast cancer	Hypothesis like immune mediated destruction of cardiomyocyte, HER-2 blockade on heart	Reduced LVEF, Heart failure	[26,27]
Bevacizumab	VEGF	Metastatic breast cancer Renal cancer Colorectal cancer	Reduce endogenous nitric oxide Vasoconstriction	Hypertension	[28]
		Tyrosine kinase inhibitor			
Dasatinib	Bcr-Abl, PDGFR-a c-KIT	Chronic myeloid leukemia	Vascular cardiac fibrosis, Myocardial necrosis, Cardiac hypertrophy and inflammation (Preclinical study)	QT prolongation , Hypertension	[29]
Imatinib mesylate	Bcr-Abl, PDGFR-a c-KIT	Chronic myeloid leukemia	Mitochondrial dysfunction Apoptosis	Edema chest pain, Congestive heart failure	[30]
Sorafenib	VEGFR, PDGFR-a/b KIT, FLT3, and RAF1	Renal cell carcinoma	Myocyte cytotoxicity	Cardiac ischemia, Hypertension	[31]
Sunitinib	VEGFR, PDGFR-a/b KIT	Chronic myeloid leukemia Renal cell carcinoma Gastrointestinal stromal tumor	Mitochondrial injury Cardiomyocyte apoptosis Decrease nitric oxide production	Hypertension, Congestive heart failure, Left ventricular dysfunction	[32,33]
Lapatinib	HER2 EGFR	Breast cancer	Decrease phosphorylated ERK Myocyte damage	Decreased LVEF, Heart failure, Asymptomatic cardiac events	[34,35]

Note: HER-2: human epidermal growth factor receptor 2; EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet derived growth factor receptor; RAF: serine threonine protein kinase transforming protein; LVEF: left ventricular ejection fraction; Human mAb: human monoclonal antibody; c-KIT: cell surface receptor tyrosine kinase.

1.13 Diagnosis of cardiotoxicity

Chemotherapeutic agents stresses the cardiovascular system that resulting in cardiac dysfunction Cardiac Review and Evaluation Committee(CREC) established the following standards to confirm initial diagnosis of cardiac dysfunction (a) cardiomyopathy described by a decrease in cardiac LVEF that was either global or more severe in septum; (b) symptoms associated with Congestive heart failure (c) sign and symptoms of heart failure either S3 gallop, tachycardia, or both (d) reduction in LVEF of at least 5% to less than 55% with associated signs or symptoms of CHF or asymptomatic decline in LVEF of at least 10% to below 55%[36]. In clinical practice both invasive and non-invasive procedure followed for diagnosis of cardiotoxicity in anthracycline treated patient[37]. Invasive procedure include endomyocardial biopsy a research tool for detection of pathophysiological changes in cardiovascular disorders. Technique involves collection of small sample of endomyocardium from ventricle via catheter based bioptome. Technique utilized for early detection of anthracycline cardiotoxicity[38]. But invasive nature of this procedure limits its use in chemotherapeutic treated patients. Noninvasive procedures also employed for detection of cardiotoxicity include (a) MUGA scan or multiple gated acquisition scan is noninvasive cardiac imaging technique to calculate LVEF in anthracycline induced cardiotoxicity[39]. Major limitation of this technique is patient exposed to unnecessary radiation and unable to detect diastolic dysfunction (b) Echocardiography is diagnostic tool in cardiology for the evaluation of cardiac function and structural abnormality. Both systolic as well as diastolic parameter measured with help of echocardiography[40]. (c) ECG or electrocardiogram for evaluation of QT intervals and ST segment a surrogate marker of cardiotoxicity[41]. (d) MRI or magnetic resonance imaging is a cardiac imaging technique used to quantify left ventricular volume for assessment of cardiotoxicity[42]. Some minimally invasive techniques utilize for

early assessment and monitoring of cardiotoxicty. These technique involve estimation of cardiospecific serum biomarker. Cardiac Troponin T (cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are early predictor of cardiac dysfunction. Increased level of N-terminal pro-B-type natriuretic peptide in patient undergoing chemotherapeutic treatment depicts wall stress and myocardial dysfunction[43]. Troponin is a biomarker of choice. Troponin not only identify myocardial injury but serve as indicator to predict cardiovascular risk. Elevated level of cardiac troponin T level in patients shows reduction in left ventricular ejection fraction (LVEF). Measurement of cardiospecific biomarkers become a useful method for finding patients with increased risk of cardiotoxicity[44].

1.4 Cardiovascular events observed during cardiotoxicity

(a). Cardiomyopathy

Cardiomyopathy often seen in patients undergoing anthracycline chemotherapy. Chemotherapeutic drugs have the potential to injure cardiomyocyte and cause inflammation of pericardium. Chemotherapeutic agent like doxorubicin induce mitochondrial dysfunction by free radical generation which further activates apoptotic signaling result in cardiomyocyte apoptosis[45]. Another chemotherapeutic agent cyclophosphamide cause direct endothelial injury and myocardial necrosis which result in cardiomyopathy[46].

(b). Coronary artery spasm

Patient undergoing treatment with 5 –Flourouracil suffer from coronary artery vasospasm. In-vitro study revealed that 5-Flourouracil causes endothelium-independent vasoconstriction in vascular smooth muscles[47].

(c).Thromboembolism

Thromboembolic events observed in cancer patient undergoing treatment with chemotherapeutic agents. Chemotherapeutic agent like angiogenesis inhibitor impair coagulation system result in blood clotting and thrombus formation. Cancer patients bear increases risk of thrombosis and haemorrhage. Some life threatening hemorrhage observed in patients treated with angiogenesis inhibitor[48, 49].

(d). Arrhythmias

Chemotherapeutic drugs causes ECG abnormality like QT interval changes result in ventricular arrhythmias. Electrophysiological changes observed with help of electrocardiogram (ECG)[50]. QT interval prolongation observed in patients treated with chemotherapeutic agent like arsenic trioxide, sorafenib and sunitinib. QT prolongation and ST-T segments changes also observed in cases of late anthracycline carditoxicity[51]. Arrhythmic ECG changes like QT prolongation and the ST segment observed in 68% patients infused with 5-Flourouracil[52]. Cyclophosphamide an alkylating agent have a dose dependent effect on electrical activity of cardiac muscle result in ventricular arrhythmias. Any change in QT interval and ST segment elevation depicts Cardiac impairment by drug[53].

(e). Hypertension

Hypertension has been reported to be common comorbidity faced by cancer patients. Chemotherapy induced hypertension generally exist in patients exposed to angiogenesis inhibitor. Condition of patient with preexisting hypertension worsen with the use of this medication. Antiangiogenic inhibitor like monoclonal antibody bevacizumab and tyrosine kinase inhibitor like sunitinib malate and sorafenib plays important role in induction of hypertension in cancer treated patients. Alkylating agents and calcineurin also induce hypertension by endothelial dysfunction and arterial vasoconstriction[54]. Mechanism of hypertension associated with angiogenesis inhibitors supposed to be reduced production of endothelial nitric oxide (NO) in arterioles and other resistance vessels. In normal VEGF enhance NO synthesis via phosphorylation of endothelial NO synthase (eNOS) which acts on endothelium produces vasodilation and reduce blood pressure. VEGF inhibition reduces NO synthesis decreased NO synthesis promotes vasoconstriction and hypertension[55].

1.5 Treatment and propylaxis aspect of cardiotoxicty

Several prophylaxis and treatment approaches employed for prevention of cardiotoxicity due to chemotherapy include:

(a). Early assessment of preexisting medical condition

In order to promote better cancer therapy active management of pre-existing cardiac complication done in patient[56]. Patient undergoing chemotherapy with pre-existing cardiac complication are more prone to cardiotoxicity. Clinical assessment of cardiac complication in such patients done before chemotherapy by evaluating LVEF, serum biomarkers such as Troponin, B Natriuretic peptides and cardiac imaging via ECG, ECHO and radionuclide angiography reduces risk of cardiotoxicity[57].

(b). Reducing and dividing the dose of chemotherapeutics

Some chemotherapeutic agent shows dose depependent cardiotoxicity. Reduction of dose reduces the risk of cardiotoxicity. In a case study of 135 patient with advanced breast cancer, patient treated with epirubicin doses between 500-1000 mg/m^2 developed less chances of congestive heart failure as compared to patient receive dose in a range 1000-1563 mg/m^2 of epirubicin[58].

(c). Change in formulation

Modified chemotherapeutic formulation with improved therapeutic index, pharmacokinetic profile and bioavailability reduces the extent of cardiotoxicity. Liposomal formulation of anthracycline derivative is less cardiotoxic as compared to the active agent. Clinically approved pegylated liposomal formulation Caelyx (Canada and Europe) or Doxil (United States) and Non-pegylated liposomal formulation Myocet (Cephalon) are used in the treatment of metastatic breast cancer[59]. A randomize clinical trial on metastatic breast cancer patients showed that liposomal formulation myocet had improve the therapeutic index of doxorubicin with preserved antitumor activity[60].

(d). Use of less cardiotoxic analogue

Development of new anthracycline analogs reduces risk of cardiotoxicity. Epirubicin an epimer of doxorubicin is significantly less cardiotoxic with antitumor activity equivalent to doxorubicin. Cardiotoxicity appears in patients receiving higher cumulative dose up to 900 mg/m^2[61]. Idarubicin synthetic derivative of daunorubicin shown to be less cardiotoxic than daunorubicin and doxorubicin used in the treatment of metastatic breast cancer and leuakemia[62]. Cardiomyopathy observed in patient receiving cumulative dose of idrarubicin upto 290 mg/m^2[14].

(e). Use of cardioprotective agent

Cardioprotective agents plays an important role in the treatment of cardiotoxicity a number of cardioprotective agents used to treat cardiac complications occurred during cardiotoxicity without losing antitumor activity. Cardioprotective agents classified on basis of their action:

- **Cardioprotectants preventing oxidative stress**

A number of antioxidants and chelating agents prevent chemotherapy induced oxidative stress. Dexarazoxane an iron chelator coadministered with anthracyclines dose to cardiotoxicity in patients in a number of randomized trials[63]. Dexarazoxane reduces the formation of anthracycline-iron complex thus prevent oxidative stress. Dexarazoxane enhance the antitumor activity of anthracyclines when given in combination[64]. Probucol is a lipid lowering drug, preclinical study suggested that probucol attenuates Adriamycin induced oxidative stress by increasing activity of antioxidant enzymes like superoxide dismutase (SOD) and glutathione (GSH)[65]. L carnitine a quartenary ammonium compound prevent oxidative stress induced cardiomyopathy and reduces apoptosis of cardiomyocyte by doxorubicin in pre-clinical studies[66]. Oral Glutamine is a non-essential amino acid, animal study suggested that oral Glutamine prevent cyclophosphamide induced oxidative injury by rate limiting synthesis of glutathione GSH[67]. DL-alpha-lipoic acid reduces cyclophosphamide induced oxidative stress by free radical scavenging activity and increased production of antioxidants in animal model[68]. Flavanoid compounds plays an important role in the management of chemotherapy induced oxidative stress. 7-mono-O-(β-hydroxyethyl) rutoside (monoHER) and Quercetin antioxidant flavonoid reduce anthracycline induced oxidative stress, in vitro study revealed that both of these flavonoid converted to quinone in order to scavenge free radicals[69].

Cardioprotective agent treated heart failure and hypertension

Angiotensin-converting enzyme inhibitors (ACEi) plays an Important role in management of congestive heart failure, myocardial infarction and hypertension, Preclinical studies suggested that ACEi like zofenopril and lisinopril exerts cardioprotective effects by modulating renin angiotensin system , maintain calcium homeostasisis and enhancing nitic-oxide synthesis[70]. Nebivilol cardiospecific beta blocker with mild vasodilating activity used in treatment of hypertension. Animal study revealed that nebivilol exerts cardioprotection against anthracycline cardiotoxicity[71]. Carvedilol is a nonselective beta blocker and alpha-1 blocker used in treatment of congestive heart failure, Clinical study revealed that antioxidant nature of carvedilol exerts cardioprotection by preventing anthracycline induced left ventricular dysfunction in child patients of acute lymphoblastic leukemia[72].

- **Cardioprotective agent treated thromboembolic events**

Cohort study revealed that low molecular weight heparin, warfarin and aspirin used for the management of venous thromboembolism in myeloma patients[73]. Clinical study showed there is a reduced risk of development of venous thromboembolism in breast cancer patient receiving low dose aspirin[74].

1.6 Role of cardio-oncolgy

Cardioncology is a new inter-disciplinary area of research generally focused on the management and treatment of rising group of cancer patients affected by concomitant cardiovascular disorders or cancer patients who are exposed to increase risk of cardiovascular complications with therapy[2]. Cancer therapy get worse with development of cardiotoxicity in cancer treated patients. For successful management of cancer therapy with cardiovascular complication in patients oncologist and cardiologist must work together. Collaboration in between cardiologist and oncologist necessary for evaluation of cardiovascular risk in patient before start of chemotherapy[75]. Assessment of various parameters like LVEF, Cardiac Imaging using echocardiography, Electrocardiographic changes using electrocardiogram and serum biomarkers like troponins and natriuretic peptides for successful management of cancer patients with cardiac disease. Few guidelines present for the prevention, diagnosis, and treatment of cardiac complication in

chemotherapy treated patients. Clinical practice guidelines of cardioncology come in to force in order to enhance long term survival of cancer patients[76]. Cardio-oncologist need to understand biology of cancer for development of chemotherapeutic agent with less cardiotoxicity[77].

2.0 Conclusion

Early detection of cardiotoxicity in cancer patient is a crucial statergy for successful management of cancer patient. Teamwork in between cardiologist and oncologist necessary for improving quality of life of cancer patient. New chemotherapeutics with better therapeutic index developed in order to practice best medicine for patients.

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