Cardiotoxicity induced by anti-cancer drugs

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ABSTRACT

Cardiotoxicity induced by anti-cancer drugs is one of the most disappointing draw backs when it comes to offering the optimal management to cancer patients. This essay aims at highlighting the types of anti-cancer drugs affecting the heart and how to minimize such effects. It will also discuss the proper methods of assessing the cardiac functions throughout the course of treatment and afterwards. Cardio-Oncology partnership is important for better quality of life for cancer patients.

Keywords: Cardiotoxicity - Anti-cancer - Chemotherapy

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ABBREVIATIONS

ACC: American College of Cardiology

ACE-I: Angiotensin Converting Enzyme- Inhibitor

ADCC: Antibody Dependant Cell medicated Cytotoxicity

AHA: American heart association

AMPK: 5' Adenosine Monophosphate-activated Protein Kinase

ARBs: Angiotensin Receptor Blockers

ATP: Adenosine Triphosphate

BMI: Body Mass Index

BNP: Beta Naturetic Peptide

Ca^{+2}: Calcium

CAD: Coronary Artery Disease

CHF: Congestive Heart Failure

CRCD: Chemotherapy Related Cardiac Dysfunction

CVS: Cardiovascular system

DNA: deoxy ribonucleic acid

E/A ratio: peak early atrial/peak late atrial velocities

EC: endothelial cells

ECG: Electro cardiogram

EDV: End diastolic volume

EGFR: Epithelial Growth Factor Receptor

EPR: Enhanced permeability retention

ESV: End Systolic Volume

FDA: Food and Drug Adminstration

Fe^{+3}: Ferric Iron

HER2: Human Epidermal growth factor receptor

HF: Heart Failure

HTN: Hypertension

IL-2: Interleukin-2

IV: Intravenous

LVD: Left ventricular dysfunction

LVEF: Left Ventricular Ejection Fraction

MAPK: Mitogen Activated protein kinase

mtCK: mitochondrial creatine kinase

MUGA: multi-gated acquisition scan

NADPH: Nicotinamide adenine dinucleotide phosphate

NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells

NO: Nitric Oxide

NRG-1: Neuregulin-1

NYHA : New York Heart Association

PARP: Poly (ADP-ribose) polymerase

PCr : Phosphocreatine

PI3K: Phosphatidyl Inositol 3-Kinase

PVCs: Premature ventricular complexes

rhNRG-1: recombinant Neuregulin-1

RNS: Reactive Nitrogen Species

ROS: Reactive Oxygen Species

SPECT: Single Photon Emission CT

Tc^{99m}: $Technitium^{99m}$

TKIs: Tyrosine Kinase Inhibitors

TNF- α: Tumor Necrosing Factor - α

Topo-II: Topo-2 Isomerase Inhibitor

VEGFR: Vascular Endothelial Growth Factor Receptor

VT: Ventricular Tachycardia

VTE: Venous thromboembolism

Introduction & Aim of work

Introduction:

Major successful leaps in anti-cancer treatment came to be true but on the expense of intensifying the chemotherapeutic protocols that lead to expanding the toxicity profile and undesirable side effects. Modern clinical pharmacy has been of a great help to manage these side effects, but when it comes to impairment of a vital organ like the heart that is a great problem.

Cardiotoxicity induced by anti-cancer drugs is one of the most disappointing draw backs when it comes to offering the optimal management to cancer patients. Certain types of chemotherapeutic agents can induce cardiac dysfunction in several ways from simple hypotension, hypertension, dysrhythmias, thromboembolism, ischemia, cardiomyopathy up to congestive heart failure (***Yeh ET.2006)***. Scientists are working hard in identifying the cardiotoxic chemotherapeutic agents, their mechanisms of action, factors increasing the cardiotoxicity and how to diagnose, manage and prevent such sequel (***Pai VB, Nahata MC.2000)***. New chemotherapeutic agents, targeted therapies and even radio-active labeled molecules are being engineered to match every patient's unique diagnosis and needs with as little side effects as possible, hence a better quality of life.

Anthracyclines are the most harmful chemotherapeutic agent on the heart and it specifically affects the myocardium leading to dilated cardiomyopathy that ends up in congestive heart failure (***Lefrak E, Pitha J,et al.1973)***. Special attention should be made to the total cumulative dose, infusion

rate, dose schedule and other concurrent cardiotoxic agents. Trastuzumab potentiates the cardiotoxic effect of Anthracyclines, so it should not be given concurrently. It has the advantage of causing non-morphological myocyte damage, in that way its cardiotoxicity is reversible upon its discontinuation (***Ewer MS, Vooletich MT, et al.2005).*** Hormonal treatment that is associated with cardiotoxicity includes tamoxifen that causes venous thromboembolic events and the aromatase inhibitors such as letrozole via hyperlipidemia. Other more recent anti-cancer drugs are associated with cardiac toxicity like Imatinib, Sorafenib and Sunitinib.

The etiology of chemotherapy induced cardiotoxicity is still under investigations, but some of the well known mechanisms include its powerful ability in generation of toxic free radicals with its consequent destructive effects that is of course applicable on both normal and tumor cells. The formation of a ferric-doxorubicin complex greatly increases free radicals formation as well (***Gianni L, Myers CE. 1992)***. Other mechanisms include cytokine formations and chemotherapy mediated apoptosis. Proper clinical examination and thorough investigations should be done to patients whom are about to receive a cardiotoxic agent, especially those at risk. Chemotherapy induced cardiotoxicity is very hard to treat, therefore cardiac functions should be given priority whenever a cardiotoxic agent is included in the course of treatment and it should be monitored carefully with a baseline, inter-cyclic and after treatment assessment. Echocardiography and multiple gated acquisition scintigraphy scan (MUGA) are the most commonly used imaging techniques to monitor the Left ventricular Ejection Fraction (LVEF) and investigate the cardiac condition prior to and after a cardiotoxic chemotherapeutic agent is administered (***Jannazzo A, Hoff man J,et al.2008, Ewer MS, Lenihan DJ.2008***). Biological markers like Tropnin I and B-type naturetic peptide (BNP) are showing promise in eliciting ventricular injury before it could be noticed by modern imaging techniques

(***Dolci A , Dominici R ,et al.2008***). A LVEF below 55% is a contraindication for chemotherapeutic agents known to induce cardiotoxicity, particularly in patients with prior history of cardiac disease in order not to worsen the condition. If necessary, certain prophylactic measures and cardio-protective agents should be used with a very close monitoring of the cardiac functions.

Using Anthracycline analogs or liposomal forms decrease the cardiotoxicity with comparable results (***Ewer MS, Martin FJ,et al 2004, Safra T, Muggia F,et al.2000***). Dexrazoxane is a cardioprotective agent that has proven to reduce the impact and severity of anthracycline-induced cardiotoxicity and it does not interfere with its antitumor efficacy (***Marty M, Espié M, et al. 2006)***. Angiotensin Converting Enzyme Inhibitors (ACE-I), Angiotensin Receptors Blockers (ARBs), Carvedilol and others are under ongoing investigations with promising results towards solving this problem (***Cardinale D, Colombo A,et al. 2010, Kalay N, Basar E,et al.2006)***.

AIM OF WORK:

The current study aims at highlighting the types of anti-cancer drugs affecting the heart, how do they affect the heart and how to minimize such sequel. It will also discuss the proper methods of assessing the cardiac functions throughout the course of treatment and afterwards. New evolving strategies to decrease cardiotoxicity are on the horizon and most importantly, the beginning of a Cardio-Oncology partnership for a brighter future for better quality of life for cancer patients.

CHAPTER ONE

Spectrum of Cardiotoxicity Associated With Anticancer Treatment

Heart disease and cancer are the two leading causes of death in developed countries ***(CDC 2010)***. To a large extent, both are associated with advancing age; consequently, patients with malignancy often either have overt cardiovascular problems or they are at increased cardiovascular risk. In addition, malignancy and its treatment places stress on body systems that are often already compromised by underlying primary cardiac or pulmonary disease. The cardiac effects of cancer treatment represent a diverse group of responses to chemical, biological, physical, and hormonal agents. The risk of serious toxicity is related to the type of agent, but is influenced by the stability and reserves of the patient's heart. The cardiovascular system has a limited number of potential responses to normal or harmful stimuli; interestingly, all of these potential cardiac responses to toxicity have been observed as a result of cancer or its treatment.

Initially, the heart can respond with a decrease in left ventricular systolic function. This may be caused by myocyte loss, which is generally permanent, or it may be because of a functional loss of the contractile elements within the cell that results in a transient, reversible decrease in systolic function. Although left ventricular dysfunction is often considered the most important end effect of cardiotoxic anticancer treatment, other squeals may also be encountered. Some treatments are associated with coronary vasospasm and can result in myocardial ischemia or, if prolonged or severe enough, may progress to myocardial infarction. Other cardiotoxic effects include arrhythmias of various types, abnormalities in the

cardiac structure such as pericardial inflammation or thickening, and valvular abnormalities are also possible ***(Yeh ET. 2006)***.

There are two types of chemotherapy related cardiac dysfunction (CRCD), Type-1 that is associated with LVEF dysfunction, and Type-2 through transient functional loss of the contractile elements within the cell that in turn causes a reversible decrease in LVEF. Later on, other cardiotoxic effects will be highlighted in brief ***(Ewer MS, Lippman SM. 2005)***. Various responses, along with the most common cancer treatments are presented in a table format (Table 1)

Table 1. Antineoplastic agents associated with Cardiac Dysfunction ***(Ewer SM, Ewer MS.2010)***

Type 1 CRCD (associated with left ventricular dysfunction)	**Anthracyclines:** • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin • Pirarubicin **Liposomal formulations:** • Daunorubicin liposomal • Doxorubicin liposomal **Anthraquinones**: • Mitoxantrone **Potential type 1 toxicity intensifiers**: • Cyclophosphamide • Ifosfamide • Mitomycin C • Etoposide • Melphalan