Cardiotoxicity induced by anti-cancer drugs

Essay Submitted in partial fulfillment of master degree in Clinical Oncology

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# CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledgement</td>
<td>4</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>5</td>
</tr>
<tr>
<td>List of Tables</td>
<td>6</td>
</tr>
<tr>
<td>List of figures</td>
<td>7</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>8</td>
</tr>
<tr>
<td>Introduction &amp; Aim of Work</td>
<td>10</td>
</tr>
</tbody>
</table>

## CHAPTERS:

1- Spectrum of Cardiotoxicity Associated With Anticancer Drugs............14

2- The Cardiotoxic effect of Anti-cancer drugs on the myocardium...........18

[A] Type 1 Chemotherapy-Related Cardiac Dysfunction (CRCD)................20

   I. Natural history of Anthracyclines.......................................23
   II. Anthracycline Type 1 Cardiotoxicity....................................25
   III. Mechanisms of Type 1 Cardiotoxicity...................................27

IV. Risk Factors for Type 1 CRCD..................................................40

[B] Type 2 Chemotherapy-Related Cardiac Dysfunction (CRCD) ...............42

   I. Anti- HER2 (Trastuzumab, Lapatinib)......................................43
      • Trastuzumab.............................................................................43
      • Trastuzumab in combination with anthracyclines.....................44
      • Trastuzumab and lapatinib ..................................................45
   II. ANTI-VEGFR (bevacizumab, sunitinib, sorafenib)......................59

3- Cardioprotection Strategies for risk reduction...............................53

   I. Reduction of risk factors.......................................................53
   II. Reduction of the cardiotoxic cumulative dose............................54
   III. Modification of the dose schedule and mode of administration.....56
   IV. Using less cardiotoxic anthracycline analogues..........................59
   V. Unique Delivery System..........................................................59
VI. Cardio-protective agents ................................................................................. 62
VII. Hemodynamic Optimization ........................................................................... 63

4- Assessing and Monitoring the Cardiotoxicity .................................................. 64
   I. Cardiac Biopsy ................................................................................................. 64
   II. Left Ventricular Ejection Fraction .................................................................. 66
   III. Biochemical Markers ..................................................................................... 72
   IV. Endothelial and pro-inflammatory markers .................................................... 74

5- Managing Heart Failure induced by anti-Cancer Drugs ..................................... 78
   I. NYHA, ACC/AHA guidelines .......................................................................... 78
   II. BNP guided therapy ....................................................................................... 83
   III. Recombinant NRG-1 therapy ........................................................................ 85

6- Other Cardiotoxic Effects .................................................................................. 90
   I. Myocardial Ischemia ....................................................................................... 90
   II. Systemic Hypertension .................................................................................. 92
   III. Thromboembolic Disease ............................................................................. 94
   IV. Arrhythmias .................................................................................................. 97

7- The Need for Cardio-Oncology Partnership ...................................................... 100

Summary & Recommendations ............................................................................. 106
References ............................................................................................................ 109
Arabic Summary .................................................................................................. 143
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Wafaa Abdel-Hadi
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
# List of Tables

<table>
<thead>
<tr>
<th>Table number</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Antineoplastic agents associated with Cardiac dysfunction</td>
<td>14</td>
</tr>
<tr>
<td>(2) Type 1 vs Type 2 CRCD</td>
<td>18</td>
</tr>
<tr>
<td>(3) MDACC data on the incidence of LVD</td>
<td>21</td>
</tr>
<tr>
<td>(4) Risk factors for increased cardiotoxicity of Type-1 agents</td>
<td>40</td>
</tr>
<tr>
<td>(5) Cardiotoxicity in relation to cumulative dose</td>
<td>54</td>
</tr>
<tr>
<td>(6) Different application modes of anthracyclines</td>
<td>58</td>
</tr>
<tr>
<td>(7) Strategies for early detection of CRCD</td>
<td>76</td>
</tr>
<tr>
<td>(8) Systems used to classify or describe HF (NYHA,ACC/AHA)</td>
<td>78</td>
</tr>
</tbody>
</table>
## List of Figures

<table>
<thead>
<tr>
<th>Figure number</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The cell cycle phases</td>
<td>24</td>
</tr>
<tr>
<td>2. Illustrating the mitochondrial membranes and structures</td>
<td>31</td>
</tr>
<tr>
<td>3. Chemical structure of doxorubicin &amp; related redox cycling</td>
<td>34</td>
</tr>
<tr>
<td>4. Role of free radicals in the pathogenesis of anthracycline cardiomyopathy.</td>
<td>36</td>
</tr>
<tr>
<td>5. Mechanism &amp; targets of Doxorubicin cardiotoxic action</td>
<td>38</td>
</tr>
<tr>
<td>7. Lapatinib preserves the cardiomyocyte contractile function.</td>
<td>49</td>
</tr>
<tr>
<td>8. Cumulative probability of developing doxorubicin induced CHF</td>
<td>55</td>
</tr>
<tr>
<td>9. The structure of a liposome for drug deliver</td>
<td>61</td>
</tr>
<tr>
<td>10. Enhanced permeability and retention effect of liposomal delivery</td>
<td>61</td>
</tr>
<tr>
<td>11. Comparison of carvidelio-LVEF at baseline &amp; after chemotherapy</td>
<td>63</td>
</tr>
<tr>
<td>12. Morphological changes of biopsy after doxorubicin exposure</td>
<td>65</td>
</tr>
<tr>
<td>13. Targeted cardiac imaging with Trastuzumab</td>
<td>71</td>
</tr>
<tr>
<td>14. The cytokine hypothesis of Heart failure</td>
<td>75</td>
</tr>
<tr>
<td>15. Stages of development of HF and recommended therapy by stage</td>
<td>82</td>
</tr>
<tr>
<td>16. Treatment modifications with BNP guided therapy</td>
<td>84</td>
</tr>
<tr>
<td>17. The primary outcome for BNP guided therapy</td>
<td>85</td>
</tr>
<tr>
<td>18. Effect of recombinant Neuregulin therapy on Heart failure</td>
<td>86</td>
</tr>
<tr>
<td>19. Evaluation of change in LVEF% after rh-NRG1 therapy</td>
<td>87</td>
</tr>
<tr>
<td>20. Incidence of heart diseases &amp; cancer in the physician health study</td>
<td>101</td>
</tr>
</tbody>
</table>
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
Ca²⁺: 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
Fe³⁺: 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-$\alpha$: Tumor Necrosing Factor - $\alpha$
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, Voolietich 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, Hoffman 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 \((Ewer \ SM, \ Ewer \ MS.2010)\)

<table>
<thead>
<tr>
<th>Type 1 CRCD (associated with left ventricular dysfunction)</th>
<th>Anthracyclines:</th>
</tr>
</thead>
<tbody>
<tr>
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<td>• Daunorubicin</td>
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<td></td>
<td>• Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>• Epirubicin</td>
</tr>
<tr>
<td></td>
<td>• Idarubicin</td>
</tr>
<tr>
<td></td>
<td>• Pirarubicin</td>
</tr>
<tr>
<td>Liposomal formulations:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Daunorubicin liposomal</td>
</tr>
<tr>
<td></td>
<td>• Doxorubicin liposomal</td>
</tr>
<tr>
<td>Anthraquinones:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mitoxantrone</td>
</tr>
<tr>
<td>Potential type 1 toxicity intensifiers:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cyclophosphamide</td>
</tr>
<tr>
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<td>• Melphalan</td>
</tr>
</tbody>
</table>