**Effect of Cytotoxic Drug (Doxorubicin) on Cardiovascular system in patients with breast cancer in Najaf**

Yesar M H . Al-Shamma* M BChB, Ph.D (UK )
Talib H. Kammona** M BChB, DM, CABM ,
Amena AB Al-Dejaily* M BChB, M Sc.

*Department of Physiology Kufa College of Medicine
**Department of Medicine Kufa College of Medicine.

Abstract:
This study was carried out to investigate the effect of cytotoxic drug (Doxorubicin) on cardiac toxicity and on haemodynamic variables during the course of treatment of patient with breast cancer with no history of cardiac diseases using totally non-invasive techniques i.e Echocardiography for the estimation of left ventricular ejection fraction [LVEF], fraction shortening [FS] and stroke volume [SV].Mercury sphygmomanometer for measuring of blood pressure and electrocardiography for the measurement of heart rate [HR] also for the evaluation of patient cardiac status.

39 patients were divided into two ages groups group I with ages range from 29-44 years and age group II with ages range from 45-60years.

In each group the doses of Doxorubicin (60 mg/m2) were increased every 21 days.
The results of this study indicate that in both age groups there was a significant decrease in LVEF, FS, SV and CO due to an adverse effect of cytotoxic drug (Doxorubicin) on cardiac muscle with subsequent treatment with this drug.

Concerning the comparison of the effect of Doxorubicin on both age groups. The results indicate that SV and CO were significantly lowered in the older age group Π than in the younger age group Ι.

Introduction:
Because cancer is leading a cause of mortality in the world. The number of therapeutic modalities available for the treatment of neoplastic processes has increased. historically, it has been well recognized that antineoplastic agent may have an adverse effect on multiple organs and normal tissues.(1)

Many chemotherapeutic and biological agents as well as irradiation have been reported to have adverted effect on the heart, the most important of these drugs is Anthracycline.(2)

Doxorubicin is ratorious for causing Cardiotoxicity This Cardiotoxicity may be caused by many factors, which may include interference with ryanodine receptor of sarcoplasmic reticulum in the heart muscle cells, free radicles formation in the heart or from the build up of metabolic products of Anthracycline in the heart. The Cardiotoxicity often present as electrocardiographic changes and Arrhythmias or as Cardiomyopathy leading to congestive heart failure [CHF] these Cardiotoxicity is related to patient cumulative life time dose. A patient life time dose is calculated during treatment, and Anthracycline treatment is usually stopped upon reaching the maximum cumulative dose.The total cumulative dose is limited to 400---550 mg/m2.(3)

Dexrazoxana is a cardioprotectant agent that is some time used to reduce the risk of Cardiotoxicity, liposomal formation of Daunorubicin and doxorubicin have been approved to appear to be somewhat less toxic to cardiac tissue.(4)

The diagnosis of Anthracycline cardiac dysfunction is generally made by comparing baseline electrocardiography finding and echocardiography study by measuring systolic function, left ventricular ejection fraction[LVEF] and fraction shortening[ FS] in patients treated with doxorubicin with breast cancer. Echo study assess the left ventricular regional wall motion, left ventricular end diastolic and end systolic dimension, FS or left and right systolic time interval index.(5)

Doxorubicin Cardiotoxicity was closely coupled to the cumulative dose, with a dramatic increase with advancing age and a striking variation in individual susceptibility, possibly reflecting inherent differences.

Doxorubicin induced a threatening, slowly progressive Deterioration of cardiac function with a displaced onset of 3 months or more after drug administration

Cardiotoxicity was primarily unmasked in the post Anthracycline period, contining many months after treatment. The more sever the Cardiotoxicity the longer time for its expression. At a cumulative dose of 850-1000mg/m2 doxorubicin, an actuarial estimation of 15% of the patients experienced a 25% relative reduction in LVEF 3weeks after terminating therapy, increasing to 59% after 3 years. One year after terminating doxorubicin therapy, 11% of the patients deteriorated into a severely dilated congestive heart failure [CHF], increasing to 20% after 5 years.(6)
The cardiotoxic effects of the doxorubicin anthraquinone have been consistently associated with free radical generation.\(^7\)

Patients treated with Anthracycline may serve as a model for studying the pathophysiological processes of anthraquinone free radical – induced damage in the healthy intact human heart, providing us with the rare opportunity to analyze the time windows for these functional damages. Anthracycline–induced Cardiotoxicity resembles the Cardiotoxicity caused by the burst of free radical formation after activated phagocytic activity following myocardial infarction, or after reoxygenation and reperfusion of.

Ischemic tissues following thrombolytic therapy or other revascularization procedures.\(^8\)

Smoking similarly causes a severe oxidative stress, with the principle radicals being anthraquinone held in tarry matrix that increase the risk of cardiovascular disease, especially in women.\(^9\)

Female sex is in general associated with a remarkable, about two –folds, increase in cardiac morbidity and mortality once a cardiac risk factor is established. This increase in female susceptibility is observed after Anthracycline therapy, with cigarette smoking and during aging. In the present study of female patients we found age to be the most dominant factor, increasing Anthracycline Cardiotoxicity susceptibility. The same age - dependent increase in susceptibility to heart damage is seen in idiopathic, dilated Cardiomyopathy. It has been suggested that many of aging processes themselves are the result of long –sustained tissue abuse by free radicals with a reduced amount of protective antioxidants in the old and the sick.\(^10\)

Method & Materials:

The study sample are the patients with first sign of breast cancer were referred for first line Anthracycline based therapy with adequate hematological, hepatic and renal function and no history of heart failure or myocardial infarction with age ranged between 29-60 years old. At initiation of the monitoring programs, all patients had monotherapy with Anthracycline, aiming at a high cumulative dose not exceeding 550mg/m\(^2\). All patients referred to our department from May 2006 through July 2007 satisfying the above criteria were asked to participate. The patients are divided into two groups: young age group whose age ranged between 29-44 years and old age group whose age ranged between 45-60 years. The details of anthropometric data of both groups are presented in table 2, 3.

Table (1): Anthropometric data for age group 1, age [29-44 years] [mean ± S.D]

<table>
<thead>
<tr>
<th>Anthropometric data</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>37.35±4.53</td>
</tr>
<tr>
<td>Sex</td>
<td>All females</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>71.14±9.76</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>153.64±5.01</td>
</tr>
<tr>
<td>BSA [m²]</td>
<td>1.71±0.05</td>
</tr>
</tbody>
</table>
Table (2): Anthropometric data for age group Π, age [45±60 years]

<table>
<thead>
<tr>
<th>Meaun ± SD</th>
<th>n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>2.19±0.35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aa</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [years]</strong></td>
<td>52.88±5.29</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>All females</td>
</tr>
<tr>
<td><strong>Weight [kg]</strong></td>
<td>74.88±8.24</td>
</tr>
<tr>
<td><strong>Height [cm]</strong></td>
<td>150.48±5.77</td>
</tr>
<tr>
<td><strong>BSA [m²]</strong></td>
<td>1.78±0.07</td>
</tr>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>2.02±0.22</td>
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</tbody>
</table>

Study was performed by a protocol determined by using Kretz technique type and model 530D with 2-4 MHZ transducer made in Australia in 1996 for measuring S.V,LVEF and FS.

The standard conventional sphygmomanometer and stethoscope used for measuring of blood pressure.

Mean blood pressure calculated by using equation [MBP] calculated as diastolic blood pressure plus one third of pulse pressure [difference between systolic blood pressure and diastolic blood pressure] as in equation;

\[
MBP = D + \frac{1}{3}(S-D)
\]

(11)

The weights of the patients are performed by using well calibrated digital weight and height scale measuring device model 1986, made by Jookad Company, Japan.

BSA in [square meter] m² as an index of body surface area calculated according nomogram of Dubois.(12)

BMI are calculated by the following equation

\[
BMI = \frac{\text{weight [kg]}}{\text{height [m²]}}
\]

(13)

Electrocardiography:

Study was performed by an instrument Mac 500 3 channels technology made in India 2006.

Assessment of the effect of Doxorubicin on cardiovascular system using totally non-invasive technique;

Throughout the entire study non-invasive techniques only were used for the assessment of blood pressure, cardiac output and heart rate.

Non-invasive methods were used in this study, partly because of the convenience and the greater acceptability from the point of view of the subject but also there is some evidence that invasive procedures may, in fact, change the haemodynamic variables which are studied.Moreover, the incidence of stressful anxiety is greatly higher on using invasive procedures.

All haemodynamic variables were studied at a steady state [steady state; means that the heart rate in consecutive minute changing by less than 3 beat/min],(i.e. after 3-6 minutes of steady state, all the haemodynamic variables were measured.

The study was performed on 40 patients admitted to Al-Sader teaching hospital in a time ranged between May 2005 and July 2007 diagnosed to have breast cancer.
All patients were assessed by chest X-ray, ECG, Echocardiography and blood picture. The age ranged between 29±60 years with mean ±SD of [40 ± 4.53] years. All patients were given chemotherapy that included Anthracyclin [Doxorubicin]. Some patients received [AC] protocol in which the doxorubicin dose 60mg/m2 every 21 days, and others received [CAF] protocol in which doxorubicin dose 50mg/m2 every 21 days and then dose calculated according to the body surface area (BSA) of the patients depending on (height and weight) according to nomogram of Dubois.12 Before receiving any treatment, assessment was done including a baseline ECG, Echocardiography, blood pressure measurement and heart rate measurement at steady state.

For every patient, the blood pressure was measured by sphygmomanometer, the heart rate was measured by ECG examination, echocardiography used to measure SV, LVEF and FS. Then follow up repeated after 2 doses then after 4 doses and after patient finishing course "after 6 doses". One of the patients was excluded because she did not complete the course of treatment.

The patients where divided into two age groups;

**Age group I** {14 patients} with age range [29-44 years] with mean ± SD [37.35±4.53 years].

**Age group II** {25 patients} their ages range [45-60 years] with mean ± SD [52.88±2.9 years].Tables 2,3.

The data taken from each patient were reviewed. These included the left ventricular ejection fraction [LVEF], fraction shortening [FS], blood pressure include,"systolic and diastolic blood pressure" [SBP, DBP], cardiac output [CO], heart rate [HR], stroke volume [SV] and peripheral vascular resistance [PVR] were averaged for each assessment including baseline, after 2 doses, after 4 doses then after 6 doses.

Data analysis was performed on the data obtained from four assessments that were mentioned above and presented as mean ± standard deviation "SD" for each variable as well compared by using PAIRED T test to determine the differences between means of each variable. The differences were considered significant if p<0.05 and p ≤0.01. All calculation computation tables and graphs performed by Microsoft excel computerized program.

**Results:**

1. Effects of Doxorubicin doses on cardiovascular system in age groups I and II;

The results indicated that the left ventricular ejection fraction [LVEF %] and fraction shortening [FS %] in both age groups I and II were significantly lower in doses of G1, G2 and G3 of treatment than that of baseline [control value].

Also the value of LVEF [%] and FS [%] were significantly lower in dose G3 than that of doses in G1 and G2 with the exception that there was no significant difference in FS [%] between doses of G2 and G3 in age group I.

Also LVEF [%] and FS [%] in dose of G2 were significantly lower than that in dose of G1 with the exception that there was no significant difference in LVEF [%] between doses of G1 and G2 in age group I.

The results of stroke volume [SV] and cardiac output [CO] indicate that there was a significant decrease in [SV] and [CO] in dose G2 and G3 than that of baseline values and
a significant decrease in dose G3 than dose of G1 in both age groups [I and II] and there was no significant differences in [SV] and [CO] between doses of G2 and G1 and also between doses of G3 and G2 in both age groups [I and II].

Also there were no significant changes between dose of G1 and baseline values in both age groups [I and II] with the exception that there was a significant decrease in [SV] in dose of G1 from that of baseline only in age group II.

There was no significant differences in values of HR, MBP, and PVR in any of the doses of G1,G2 and G3 from the baseline and also no significant differences among doses of G1,G2 and G3 in both age groups [I and II].

As shown in tables:


Table [4]; The Effect of doses 2[G1], 4[G2], 6[G3] of Doxorubicin on cardiovascular system.

Table (3).A; The Effect of doses of doxorubicin in age group I

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>LVEF</td>
<td>59.71±8.19</td>
<td>53.85±6.53</td>
<td>49.85±5.24</td>
<td>44.71±5.23</td>
</tr>
<tr>
<td>FS</td>
<td>25.85±5.28</td>
<td>21.71±3.38</td>
<td>19.14±1.83</td>
<td>17.92±1.20</td>
</tr>
<tr>
<td>SV</td>
<td>78.07±5.91</td>
<td>74.14±5.94</td>
<td>71.92±5.67</td>
<td>69.07±5.91</td>
</tr>
<tr>
<td>CO</td>
<td>6.01±0.66</td>
<td>5.71±0.58</td>
<td>5.43±0.58</td>
<td>5.19±0.14</td>
</tr>
<tr>
<td>HR</td>
<td>77.07±5.52</td>
<td>77.50±4.65</td>
<td>77.78±4.97</td>
<td>77.50±0.57</td>
</tr>
<tr>
<td>MBP</td>
<td>94.00±9.75</td>
<td>89.85±10.49</td>
<td>93.57±8.34</td>
<td>94.71±8.35</td>
</tr>
<tr>
<td>PVR</td>
<td>15.80±2.07</td>
<td>16.34±2.16</td>
<td>16.73±2.17</td>
<td>17.07±2.14</td>
</tr>
</tbody>
</table>

Table (3).B; The Effect of doses of doxorubicin in age group II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>B</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF</td>
<td>61.20±9.49</td>
<td>55.92±8.23</td>
<td>50.68±7.53</td>
<td>44.88±6.79</td>
</tr>
<tr>
<td>FS</td>
<td>26.96±4.92</td>
<td>23.20±3.71</td>
<td>20.44±3.06</td>
<td>18.24±1.42</td>
</tr>
<tr>
<td>SV</td>
<td>72.04±6.56</td>
<td>68.12±6.55</td>
<td>66.00±6.72</td>
<td>62.60±7.06</td>
</tr>
<tr>
<td>CO</td>
<td>5.46±0.86</td>
<td>5.07±0.70</td>
<td>4.79±0.76</td>
<td>4.54±0.76</td>
</tr>
<tr>
<td>HR</td>
<td>75.48±6.87</td>
<td>74.56±5.15</td>
<td>75.72±4.85</td>
<td>76.48±4.80</td>
</tr>
<tr>
<td>MBP</td>
<td>88.52±12.93</td>
<td>89.20±9.46</td>
<td>88.16±12.52</td>
<td>93.04±13.90</td>
</tr>
<tr>
<td>PVR</td>
<td>16.42±3.26</td>
<td>16.73±3.24</td>
<td>16.98±3.25</td>
<td>17.18±3.22</td>
</tr>
</tbody>
</table>

LVEF; left ventricular ejection fraction [%]
FS; fraction shortening [%]
SV; stroke volume [ml]
Figure (1.A): the effect of different doses of doxorubicin on left ventricular ejection fraction group I
Figure (1.B) the effect of different doses of doxorubicin on left ventricular ejection fraction group II

Figure (2.A): the effect of different doses of doxorubicin on fraction shortening group I
Figure (2.B): the effect of different doses of doxorubicin on fraction shortening group II
Figure (3.A) the effect of different doses of doxorubicin on stroke volume group I

Figure (3.B): the effect of different doses of doxorubicin on stroke volume group II
Figure (4.A): the effect of different doses of doxorubicin on cardiac output group I

Figure (4.B): the effect of different doses of doxorubicin on cardiac output group II
Figure (5.A): The effect of different doses of doxorubicin on peripheral vascular resistance group I

Figure (5.B): The effect of different doses of doxorubicin on peripheral vascular resistance group II
Discussion:

Doxorubicin Cardiotoxicity was closely coupled to the cumulative dose with a dramatic increase with advancing age and striking variation in individual susceptibility, possibly reflecting inherent differences. Doxorubicin induced a threatening, slowly progressive deterioration of cardiac function with a displaced onset of 3 months or more after drug administration.\(^{(6)}\)

1. Hemodynamic response to different doses of Doxorubicin in both age groups:

The cardiovascular response to different doses of Doxorubicin indicate that there is highly significant decrease in left ventricular ejection fraction [LVEF] and fraction shortening [FS] with subsequent doses reaching the end of treatment course [after 6 months], which are in agreement with other investigators\(^{(2,15)}\).

The most likely reason of the changes in LVEF and FS in response to doxorubicin is that mainly due to decreasing the effectiveness of cardiac muscle pumping adequate amount of blood to the systemic circulation due to the adverse effect of cytotoxic drug on the heart muscle [i.e., the main sign regarding the main sign of Cardiotoxicity]\(^{(6)}\).

The stroke volume [SV] and cardiac output [CO] are significantly decreasing while increasing the doses of doxorubicin. This result in agreement with another previous study\(^{(6,16)}\).

The main reason for this change is the effect of cytotoxic drug on the efficiency of heart muscle lead to the decrease of venous return then decrease in stroke volume, and because the cardiac output is the product of stroke volume and heart rate, so there is a decrease in cardiac output [CO] as well\(^{(17,18)}\).

The mean blood pressure [MBP] and heart rate [HR] show no significant change in this study. This finding agrees with other observations\(^{(6)}\) while other investigators\(^{(19)}\) show significant increase in heart rate mainly after 4 doses of doxorubicin as part of a sign of Cardiotoxicity in acute stage.

The peripheral vascular resistance [PVR] in this study shows slight increase which is not significance since the peripheral vascular resistance is the product of mean blood pressure and cardiac output\(^{(20,21)}\).

2. The comparison of the differences in response to Doxorubicin between the two age groups [group I and group II]

Regarding the left ventricular ejection fraction [LVEF] and the fraction shortening [FS] in this study, it was found that there is no significant difference in these variables between group I and group II and this agrees with previous study\(^{(19)}\) which found that there was no significant difference according the age group which indicate the fact that these signs are related to cumulative dose of drug most likely than the age group\(^{(6)}\).

Regarding the stroke volume [SV] and cardiac output [CO] in this study, it was found that there are significant differences between two age groups which in is agreement with other investigators\(^{(15,19)}\) who found that there is a significant lowering in stoke volume and cardiac output in older age group than in younger age group due to attenuated autonomic nervous system in old age group in addition to adverse effect of cytotoxic on the heart muscle [i.e.; early sign of dilated Cardiomyopathy, which is common problem of Cardiotoxicity in these age groups of patients].
Regarding the heart rate [HR], mean blood pressure [MBP] and peripheral vascular resistance [PVR] also show no significant differences between both age groups which agrees with other studies. (6)

References: