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Prediction Of Anthracycline Induced Cardiotoxicity: Study Of Thirty-One Iraqi Adult Patients

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Abstract

Objective

To look for a nearly ideal tool for prediction of anthracycline-induced cardiotoxicity.

Method

Thirty-one patients with various hematological malignancies were included in the study which was conducted from Sept. 2005 to Sept. 2006 in Baghdad Teaching Hospital - Hematology Unit. Initial cardiovascular assessment including cardiac troponin I, electrocardiography and echocardiography were done and repeated one month after the commencement of anthracycline-based regimen. Cardiotoxicity was considered present if the patient has clinical and electrocardiographic evidences, troponin positivity, echocardiographic evidence, or any combination of these.

Results

The mean age for the study sample was 34.1±17.2 years comprising of 17 male and 14 female patients. Increasing age, body surface area, anthracycline dose as well as the concomitant use of cyclophosphomide/ All Trans Retinoic Acid were associated with increased risk of cardiotoxicity. The cut-off point of body surface area above which the risk of anthracycline-induced cardiotoxicity is increased was 1.88 m^2 while the cut-off point for anthracyclines dose was 145.5 mg/m^2. The constellation of clinical data, ECG, and cTnI was 92% predictive of early evidence of anthracycline-induced cardiotoxicity. More weight is added when echocardiography is used as a diagnostic tool. The incidence of cardiotoxicity attributed to treatment was 38.7%. The predictive power of cardiac troponin I alone was 58.3%, whereas it increases to 91% when combined with electrocardiography and to 95% when combined with echocardiographic study.

Conclusion

The age, anthracyclines dose and the use of other chemotherapeutics increase the risk of anthracycline-induced cardiotoxicity. Cardiac troponin I is a simple non-invasive indicator for the presence of anthracycline-induced cardiotoxicity especially when used in combination with other parameters.

Keywords

Anthracycline, Cardiotoxicity, Troponin

Introduction

Anthracyclines have been used in oncologic practice since the late 1960s. It held promise as a powerful drug in the fight against cancer. As a result of the introduction of anthracyclines, together with other improvements of treatment, cancer survival has improved markedly, particularly among children, where survival rates have increased from 30% in the 1960s to 70% currently. However, the use of anthracyclines is limited by a dose-dependent cardiotoxicity and reports of fatal cardiotoxic effects of doxorubicin have subdued enthusiasm for this drug. The most serious side effect of long-term doxorubicin treatment is cardiomyopathy followed by congestive heart failure as the prognosis for patients with this complication is grave.[1, 2]

In a study on childhood leukemia, nearly 60% of the 115 survivors had echocardographic abnormalities in heart function[3]. Congestive heart failure developed in more than 4 percent of patients who had received a cumulative dose of

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500 to 550 mg of doxorubicin per square meter[1].

Anthracyclines are widely used in cancer treatment; however their mechanisms of action, both in treating cancer and in their toxicity on the heart and other organs, are still not well understood. The majority of evidence shows that myocyte toxicity involves the generation of free radicals, through an enzymatic mechanism using the mitochondrial respiratory chain, as well as through a non-enzymatic pathway, which incorporates iron[4]. As iron accumulation increases with age, this observation has profound implications when considered along with the results presented by Miranda et al.[5]. These free radicals may continue to be generated after acute doxorubicin treatment has ceased and can account for the delayed manifestation of cardiomyopathy[6]. The standard clinical approach for monitoring doxorubicin cardiotoxicity includes assessment of base-line cardiac performance before doxorubicin therapy begins; regular monitoring during treatment and follow-up after therapy has been completed.

Electrocardiographic changes include various reversible arrhythmias, most commonly sinus tachycardia. In addition, serial echocardographic measurement of the ejection fraction is a sensitive non-invasive tool for the primary detection and follow-up of anthracyclines-induced cardiomyopathy, as well as an easy and relatively low-cost procedure. The sensitivity of ejection-fraction studies for the detection of subclinical early cardiomyopathy becomes even higher when they are combined with exercise stress testing. Therefore, study of the ejection fraction should be part of the routine care of patients receiving doxorubicin treatment.[7]

However, traditional 2D echocardiography allows measurement of various parameters of both systolic and diastolic functions, anatomic dimensions and afterload. As diastolic modifications from baseline values occur earlier in other clinical settings, there has been an increasing interest in measuring diastolic, rather than systolic, parameters to detect subclinical cardiac toxicity in patients receiving chemotherapy. Indeed, one recent study suggests that indexes of early diastolic function are predictive for the early detection of anthracyclines-associated cardiac toxicity.[8]

Cardiac Troponins have recently been applied to the early detection of chemotherapy-induced cardiac toxicity. They have shown predictive value for long-term, cumulative cardiac damage by anthracyclines and could stratify patients at different risk of cardiac events following chemotherapy based on even minimal elevations of cTnI levels recorded soon after chemotherapy and 1 month later.[9, 10]

The primary goals in prevention are to minimize cardiac toxicities and to maximize oncological efficacy. Several preventive measures are currently being used, including limiting cumulative dose, altering anthracyclines administration, using anthracyclines analogues, adding cardioprotectants to the regimen and employing nutritional supplements.[11]

Patients and Method

This study was conducted in the Haematology unit - Baghdad Teaching Hospital during the period Sept. 2005 to Sept. 2006. Thirty-one patients were recruited.

Eligibility and exclusion criteria:

1. Patients with haematological malignancies mandating treatment with anthracyclines-based regimen were included;
2. Diagnosis made by bone marrow study and/or lymph node biopsy;
3. Patients with past history of cardiac disease were excluded;
4. Patients with other organ dysfunction were excluded.

The study protocol:

The patients were interviewed with their current and past medical histories taken with special attention to past history or features of an already diagnosed heart disease plus features of other disease. Clinical examination included general examination and cardiovascular examination. Initial biochemistry and blood tests were conducted. Thorough cardiovascular assessment was initiated including ECG, CXR and Echocardiography were done looking for any subtle pathology and established as baseline

assessment before the initiation of anthracyclines-based chemotherapy. Tests for cardiac troponin I (cTi) were done for all patients initially as part of baseline assessment. A written clinical acceptance by the patients or their guardians to start chemotherapy was included in the patients' case sheets. Anthracyclines treatment alone or in combination was given according to the protocol used for the diseases. Anthracyclines doses were calculated according to the body surface area. All anthracyclines were used via an intravenous infusion over 30-45 minutes. No radiotherapy was used during this period.

The test for cardiac troponin I was repeated after thirty days again in addition to ECG and echocardiography. .

The Test for Cardiac Troponin I:

Serum sample was taken and dropped in a special troponin kit and after ten minutes we can read the results. The cut-off point of the test for cardiac troponin I was 0.5 nanogram/ml using the Acon Laboratory kit with brand name CTI-402/USA. Echocardiography was performed by a single user machine (Philips Envisor C/USA).

Definition of cardiotoxicity:

Cardiotoxicity was considered in patients if they have:

1. Clinical findings suggestive of cardiac dysfunction + ECG evidence;
2. Echocardographic evidence of cardiac dysfunction;
3. Troponin positivity; or
4. Any combination of these parameters

Statistical analysis:

Data was translated into a computerized database structure. Frequency distribution for selected variables was done first. The statistical significance of difference in mean of a normally distributed quantitative variable between 2 groups was assessed by independent samples t-test. The Chi-square test was used to assess the statistical significance of association between 2 categorical variables. A P value of < 0.05 was considered indicator of statistically significant difference. A multiple logistic regression model with several selected independent variables and the risk of developing cardio-toxicity as the dependent variable was used to assess the risk of developing cardio-toxicity in the presence of a certain risk factor (explanatory variable), while adjusting for other independent variables included in the model. The area under the Restricted Operator Characteristics (ROC) curve gives an idea about the usefulness of the test and helps in comparing it to other tests.

Results

Thirty one patients with mean age of 34.1±17.2 years were included with 17 males and 14 females. Sixteen patients (51.6%) of the study group were in the age group of 20-49 year whereas eight of them (25.8%) were more than 50 years in age. 14 patients (45.2%) had AML as their hematological diagnosis. 12 patients (38.6%) developed evidence of cardiac toxicity, with six males and six females and a mean age of 36.4 years. (Table 1) shows the demographic characteristics of these patients. The test for validity parameters of age in years when used to predict cardiotoxicity attributed to treatment revealed that 44.5 years is the age at which the risk of cardiotoxicity increases with a PPV at

Parameter	No./%
Number	12
Mean age	36.4 years
Gender	
Male	6/12 50%
Female	6/12 50%
Body Surface Area	
Range	1.6-2.2 m2
Mean	1.84m2
Optimum	1.88m2
Prior anthracycline treatment	-Ve
Prior radiotherapy	-Ve
Hematological diagnosis	8
Acute leukemia	3
NHL	1
HD	
Clinical findings suggestive of cardiac dysfunction	4/12 33.3%
Clinical findings and ECG	4/4
Clinical findings and echo findings	3/4
Clinical findings and positive troponin	2/4
Clinical findings plus echo and troponin	2/4
ECG findings suggestive of cardiac dysfunction	8/12 66.6%
ECG evidence alone	3/8
ECG and echo evidence	3/8
ECG and positive troponin	4/8
ECG plus echo and positive troponin	3/8
Echocardiographic findings suggestive of cardiac dysfunction	5/12 41.6%
Asymptomatic reduction in EF	1/5
Diastolic dysfunction	2/5
Systolic dysfunction	2/5
Troponin positivity	7/12 58.3%
Positive troponin and negative echo study	4/7
Positive troponin and positive echo study	3/7
Systolic dysfunction	2/7
Diastolic dysfunction	1/7

Table 1 : The demographic characteristics of patients who developed cardiotoxicity and their distribution according to the diagnostic modality.

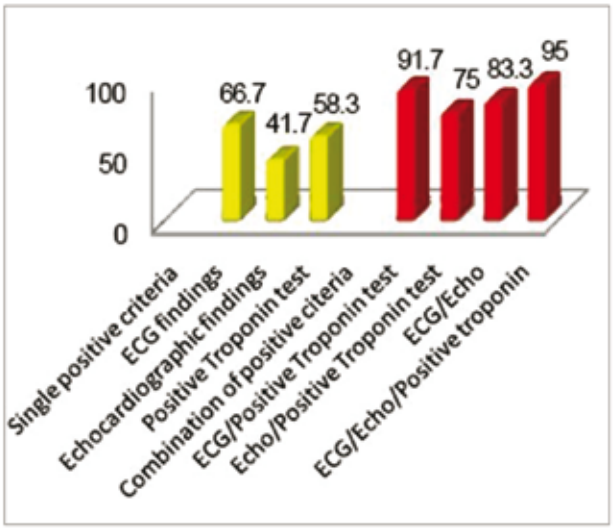

Fig.1: Bar chart showing the sensitivity rate of selected indices in predicting cardiotoxicity after treatment.

50% pretest probability of 70.9% and a PPV of 95.6% at pretest probability of 90%. A body surface area of 1.88 m^2 is the optimum point of body surface area at which the risk of treatment-related cardiotoxicity is increased with 82.6% PPV at pretest probability of 50% and PPV of 97.7% at pretest probability of 90% and a P value of 0.03 with an area under the ROC curve of 0.08. The test for validity parameters of the recommended dose schedule of Doxorubicin (mg/m^2) when used to predict cardiotoxicity attributed to treatment showed that a dose of 145.5 mg/m^2 is the cut-off point above which the risk of cardiotoxicity increase with PPV of 75.9% at pretest probability of 50% and a PPV of 96.6% at a pretest probability of 90%. In terms of the total dose (mg) it will be 282.6 mg with nearly 100% sensitivity and specificity for early development of cardiotoxicity. Three patients who used ATRA in their treatment schedule experienced events suggestive of cardiac insult. One of them showed asymptomatic reduction in EF and the other two showed clinical evidences in form of arrhythmia and the development of basal rales with an area under the ROC curve of nearly one. The validity parameters of the dose schedule of cyclophosphomide when used to predict cardiotoxicity attributed to treatment showed that PPV was 100% at both pre and post test probability in a dose of 2.625 g. Multiple logistic regression models showed that the total risk of developing cardiotoxicity for patients with body surface area of > 1.81 and using Cyclophosphamide/ ATRA is 10.6 times more than those with no such risk factors.

It is important to note that specificity was not used because not one of these diagnostic tests is the gold standard for the diagnosis of AIC and endomyocardial biopsy was not used as a diagnostic tool in this study.

Discussion

Over the last 40 years, great progress has been made in treating childhood and adult cancers. However, this progress has come at an unforeseen cost, in the form of emerging long-term effects of anthracyclines treatment. A major complication of anthracyclines therapy is its adverse cardiovascular effects. If these cardiac complications could be predicted, anticipated, reduced or prevented, higher doses of anthracyclines could potentially be used, which may increase cancer cure rates. Moreover, as the incidence of cardiac toxicity resulting in congestive heart failure or even heart transplantation dropped, the quality and extent of life for cancer survivors would improve.[11] Undoubtedly, endomyocardial biopsy obtained from the right ventricle by catheterization is considered the most sensitive and specific tool for any anatomic type of cardiac damage, but in clinical practice the use of this technique is obviously limited by its invasiveness, lack of universal expertise in obtaining and interpreting biopsy specimens and also by sampling errors due to scattered cardiac damage, especially in the preclinical phase.[12] Other standard diagnostic tools which are performed in clinical practice include ECG, chest radiography, and echocardiography. Many recent studies have elucidated the value of both troponin T and I in the diagnosis and in the risk assessment of acute coronary syndromes. Other studies addressed the question of whether cTnI measurement gives significant information in patients with hematological and solid malignancies treated with anthracyclines in relation to the possible direct cardiotoxic effect.[13] This study shows that certain baseline patients characteristics like age, gender and body surface area are related to the occurrence of AIC. The effect of the dose limit of anthracyclines was also studied and it is

clear that the higher the dose of anthracyclines, the higher the risk of developing AIC.

Other chemotherapeutics like cyclophosphomide and medications like ATRA were associated with increasing risk of developing AIC if used in combination with anthracyclines.

The collection of clinical data, ECG, and cTnI test post treatment revealed an easy and accessible way for prediction of AIC. This will have more weight by the addition of echocardographic assessment for evidence of AIC. The possibility of identifying patients at higher risk of developing late myocardial function depression could permit clinicians to modify and support cardiac function with cardiovascular therapy or cardio protective agents and to accurately monitor the progression of cardiac damage.[13] This last point is particularly relevant, considering that a progressive and cumulative cardiotoxicity occurs during anthracyclines therapy and that the risk of developing cardiac dysfunction, as revealed clinically - by ECG, by echo study and or by troponin positivity - increases in parallel with the number of cycles of anthracyclines therapy completed.

All patients received anthracyclines via an IV infusion and the effect of slow infusion to prevent AIC is still controversial but it has been postulated that the continuous infusion reduces the peak anthracyclines levels and the contrary prolongs exposure.[11] No radiotherapy had been used as all patients were in their early stages of treatment and no one gets total body or at least mediastinal radiation for acute hematological emergency. There were two shortcoming points regarding methodology: the first one is that there are other types of cTnI kits with more detective ability used worldwide but unfortunately are not available in Iraq. The other shortcoming is the small study sample which affects the statistical analysis and for the same reason affects the ROC curves used in statistical analysis to ascertain how much the test is valuable and ideal.

The technically simpler dosage of circulating markers is partly countered by the lack of knowledge about optimal timing of measurement and its potential use as a diagnostic and predictive tool also remains investigational. However, the potential for cTnI to stratify patients at risk for cardiac complications following anthracycline containing high dose chemotherapy is continually reported.[8]

The echocardographic assessment of the study group revealed that patients develop asymptomatic reduction in EF, diastolic dysfunction and overt systolic LV dysfunction. It had been stated that patients may have asymptomatic reduction in the first three months after therapy and may be associated with increased level of troponins. Patients with such increased level of troponin have long term effect of decreased EF years later. In contrast to patients with reduction in EF in the first three months but with normal cardiac troponins, this reduction will be transient and will return to normal.[13] From this it is apparent how important the integration of multiple tests in prediction of AIC. As diastolic modifications from baseline values occur earlier in other clinical settings, there has been an increasing interest in measuring diastolic, rather than systolic parameters to detect subclinical cardiac toxicity in patients receiving chemotherapy. Indeed, one recent study suggests that indices of early diastolic function are predictive for the early detection of anthracycline-associated cardiac toxicity and showed that an earlier increase in the diastolic indices abnormalities regarding LVEF or chamber dilation, and a strict correlation with risk factors, total doses and the patient outcome[8,12] A recent study conducted on 76 patients in the Royal Cornwall Hospital, UK by Belham M et al revealed that twenty-six percent of patients without significant pre-existing cardiac disease developed cardiotoxicity. The parameter that best predicted the development of functional cardiotoxicity was the change in EF between baseline and low dose with an area under the curve of 0.92 i.e., ROC curve. The Tei index detected declines in LV function earlier in the course of treatment with anthracyclines and to a greater significance than any other standard echocardographic measurement but did not predict functional cardiotoxicity.[14]

The slightly higher incidence of AIC in female was attributed to the fact that females have a larger relative fat mass, so equivalent

doses of anthracyclines could lead to higher concentrations and consequently more AIC.[4] It is apparent from the study that the higher the BSA, the more risk of AIC. This can be explained that the high BSA will be reflected by high dosage of anthracyclines and it is well-known that AIC is dose dependent. In combination with other cancer chemotherapy agents, cyclophosphomide can cause cardiomyopathy. However, the total dose of an individual course of cyclophosphomide, rather than the cumulative dose, seems to be the best predictor of acute cardiotoxicity. Previous or concomitant treatment with an anthracycline and mediastinal radiation therapy may contribute to the development of cardiotoxicity, which may include heart failure, myocarditis, or pericarditis. The mechanism of injury is thought to be related to endothelial and myocyte injury caused by a toxic metabolite.[15] Actually the use of ATRA is usually associated with cardiovascular side effects including blood pressure alterations, fluid overload and serositis that may be manifested by pericarditis. In our study group, the effect of ATRA probably enhanced the cardiotoxic effect of anthracyclines. Thus the older age group has a high BSA and the use of cyclophosphomide/ ATRA were associated with increment in the risk of AIC.

Biomarkers such as troponin I and T may be useful in the early detection of anthracyclines-induced cardiotoxicity before a reduction in the LV ejection fraction is seen. In particular, if the troponin I level shows a low grade elevation both during and after chemotherapy, the patient usually develops cardiovascular complications. Conversely, if the troponin I level remains low during chemotherapy and the ensuing months, patients have an excellent prognosis in terms of cardiac function. However, no prospective trial has shown the predictive value of such an approach.[14] Cardiac troponin I were also used as a surrogate measure of early anthracyclines-induced myocardial injury, and to assess the response to treatment like the iron-chelating agent dexrazoxane. Cardiac troponin also can be used to predict the natural history of anthracyclines-induced myocardial injury, as those patients may have asymptomatic reduction in ejection fraction the first three months after therapy that associated with increased level of troponins. Patients with such increased level of troponin have long term effect of decreased EF years later. In contrast those patients with reduction in EF in the first three months but with normal cardiac troponins, this reduction will be transient and will return to normal.[13]

Comparison with other studies:

Our data confirm previous studies reporting that cardiotoxicity due to anthracyclines is dose-related. Most of the previous studies looked for evidence of cardiotoxicity in children who completed their schedule of treatment or their doses of anthracyclines exceeded 550mg/m^2. Other group of studies conducted on adult patients assessed evidence of cardiotoxicity after HDC. However, in other studies early cardiotoxicity occurs in 1.6% to 2.1% of all anthracyclines-treated children[16,17]; also Belham et al in 2006 showed 26% of AIC in adult patients receiving high dose chemotherapy, while in this study of adult patients' early cardiotoxicity detected by different tests was 38.7%. In comparison, cTnI appears to be a sensitive, as well as a simple and low-cost, method for the identification of early, and possibly reversible, cardiotoxicity. This was nearly identical with other studies and the addition of cTnI will add more to the diagnostic accuracy of AIC. In addition, Missov et al.[18] described cTnI increase during the course of anthracyclines chemotherapy in patients with hematological malignancies. The small release of cTnI indicates that only a minimal acute necrosis occurs during anthracyclines therapy, as compared with that observed in acute coronary syndromes. However, the clinical interest of this cTnI increment is quite relevant. Indeed, the impairment in systolic cardiac function is predicted by cTnI elevation. This finding strongly amplifies the clinical significance of cTnI in order to characterize patients who will develop late cardiac impairment and to a greater extent, to predict the degree of the future left ventricular dysfunction. Some studies have looked into other biochemical evidence of AIC like plasma concentration of NT-pro-BNP which proved to be a good and easy tool for the prediction of AIC.[10]

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