CARDIAC STATUS OF LONG TERM SURVIVORS AFTER ANTHRACYCLINE THERAPY

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CERTIFICATE

This is to certify that this dissertation on "**CARDIAC STATUS OF LONG TERM SURVIVORS AFTER ANTHRACYCLINE THERAPY"** is a bonafide work done by **Dr. Prasad P. Gunari**, in the department of Medical Oncology, College of Oncological Sciences, Adyar, Chennai, under my overall supervision and guidance, to my satisfaction

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INTRODUCTION

Doxorubicin which belongs to the anthracycline family of drugs ,is a key component of chemotherapy regimens and is the most active agent for the treatment of lymphoma. However doxorubicin use is limited by its severe cardiotoxicity, including cardiomyopathy and congestive cardiac failure, which are late cardiac effects usually occurring after doses greater than 550 mg/m^2 [(1)].Early toxicity is rare and includes myocarditis, pericarditis and arrhythmias .Late cardiotoxicity after doxorubicin has largely been studied in children [(2,3)] but less often in adults. In children, the prinicipal risk factor for anthracycline cardiomyopathy is highly dependant on cumulative doses [(1-4)]. For adults few studies have been performed in the setting of breast cancer with epirubicin [(5)] or doxorubicin [(6)],of acute myeloid leukaemia after idarubicin [(7)]or after doxorubicin for various hematologic malignancies [(8,9)].For these patients, an increased risk of developing late cardiotoxicity after anthracycline treatment has been associated with advancing age or with higher cumulative doses [(4,9)].Most of these studies involved patients who received doxorubicin ranging from 450-550 mg/m^2. Altough risk factors for doxorubicin –induced congestive heart failure have been studied ,subclinical cardiac toxicity after lower doses of doxorubicin is less usnderstood .

Therefore we studied the occurrence of late cardiac abnormalities by measuring systolic function, Left Ventricular Ejection Fraction (LVEF), Fractional shortening (FS) in patients treated with doxorubicin for lymphoma .We evaluated the cardiac function of patients observed for atleast 5 years after successful treatment of the lymphoma with chemotherapy regimens including doxorubicin .

AIMS OF THE STUDY

1. To assess the cardiac status of long term survivors who previously received doxorubicin-based chemotherapy for lymphoma .

2. To analyze the risk factors for development of late anthracycline cardiotoxicity.

REVIEW OF LITERATURE

1 DEFINITION & NATURAL HISTORY OF ANTHRACYCLINE CARDIOTOXICITY

Anthracycline induced cardiotoxicity can be broadly classified by clinical presentation into three categories : acute, early onset chronic cardiomyopathy and late onset cardiomyopathy.They differ not only in their time of presentation but also in their clinical characteristics and their association with risk factors known to predispose to anthracycline induced cardiotoxicity

1.1 Acute anthracycline induced cardiotoxicity

Acute anthracycline induced cardiotoxicity is defined as a reversible depression of myocardial function after the initial infusion of anthracycline. With current protocols this type of toxicity is rare, occurring in <1 % of patients.The clinical manifestation may occur within the first week and is usually an acute but transient decrease in contractility occasionally resulting in congestive cardiac failure[14,15]. Much less frequently seen complications include myocarditis –pericarditis syndrome and acute life threatening cardiac arrhythmias, such as ventricular or supraventricular tachycardias[17-18]. Altough extremely rare, myocardial ischemia and infarction or sudden death as a result of coronary vasospasm have been reported in the first hours of therapy .

1.2 Early onset chronic progressive anthracycline induced cardiotoxicity

Usually presents within 1 year after the completion of anthracycline treatment, has known risk factors and will persist or progress even after discontinuation of therapy. The majority of adult patients who develop significant cardiotoxicity have a chronic dilated cardiomyopathy .In the pediatric patient, however, the clinical picture is as likely to become that of a restrictive cardiomyopathy on increasing follow up. This distinction is important, as it has implications not only for diagnosis but also for treatment .

1.3 Late onset chronic progressive cardiomyopathy

Defined as cardiomyopathy that manifests itself after a latency period of more than one year after completion of anthracycline therapy .With this type of cardiotoxicity, there is a period during which no left ventricular dysfunction or arrhythmias are detected, cardiac function appears normal, and patient is asymptomatic. After this latent period, there is progressive and rarely fatal deterioration in cardiac function .

2. PATHOGENESIS

Several mechanisms have been suggested to explain the pathogenesis of anthracycline induced cardiotoxicity .In most cases more than one mechanism is probably involved

2.1 Cellular level

The most frequently proposed mechanism at the cellular level involves the mediation by

oxygen radicals [26-34].There is growing evidence that the mitochondria of the cardiac myocyte may play an important role in anthracycline induced cardiomyopathy.Anthracyclines are metabolised into aglycones, the noncarbohydrate portion of a glycoside. Interaction of these aglycones with the mitochondrial membrane generates superoxide and superhydroxide free radicals and increase the permeability of the mitochondrial membrane. Because the myocardium is naturally poor in the catalytic enzymes that break down these free radicals, the radicals accumulate, eventually destroying the mitochondria .New drugs such as dexrazoxane and probucol, act to reduce the formation of these free radicals and have successfully prevented anthracycline induced cardiotoxicity in both animal and human studies [32,34-40]. Other hypothesis proposed in literature include myocyte damage from calcium overload [41-45], cellular toxicity from metabolities of doxorubicin other than aglycones [46,47], disturbances in myocardial adrenergic function [48-50], release of vasoactive amines [51-52] and elaboration of pro inflammatory cytokines [53-56]

2.2 Mechanistic level

The mechanistic changes seen are now better understood with the application of improved & more sophisticated echocardiographic techniques. For both early & late – onset types of chronic progressive anthracycline –induced cardiomyopathy, the mechanisms appear to differ for children and adults.

2.2.1 Adult versus pediatric patients

Anthracycline –associated cardiotoxicity in patients treated in adulthood has generally been described as a form of dilated cardiomyopathy, in which chronic damage to the myocardium results in a dilated poorly contractile heart. The wall of the ventricle thins and there is more stress on the heart. However a recent study of patients who received anthracyclines during childhood revealed a different pattern of myocardial damage, with decreased ventricular compliance [57]. There was an overall decrease in left ventricular dimension in relation to body surface area. This is the pattern observed in restrictive cardiomyopathy, in which the ventricle loses its ability to dilate. Echocardiographic and clinical findings suggest that the medium to long term course in anthracycline treated children may be characterised by progression of a restrictive cardiomyopathic process, resulting in a small thin left ventricle relative to body surface area. The reason for the difference in presentation between patients treated in childhood and those treated as adults is unknown, but it may be related to ongoing somatic growth in children. By 6 months of age, the heart has the adult number of myocytes & subsequent myocardial growth occurs primarily by hypertrophy of individual myocytes. In young children, it appears that anthracycline cause a dose related impairment of myocardial growth. Long term follow up studies of these patients suggest that even after cessation of therapy, there may be an ongoing loss of myocardial cells. The myocardial growth failure, loss of myocardial cells, or both may contribute to the striking decrease in left ventricular mass in some of these patients [58,59]

3 RISK FACTORS FOR ANTHRACYCLINE –INDUCED

CARDIOTOXICITY

In the last 10 years, major progress has been made in identifying risk factors for anthracycline –induced cardiotoxicity. These risk factors relate to early and late but not acute cardiotoxicity. Risk factors for anthracycline – induced cardiotoxicity in decreasing order of importance [134]

3.1 Cumulative dose

Total cumulative anthracycline dose is well established as a risk factor for cardiac damage. In a study examining the late cardiac effects of doxorubicin therapy in children with ALL, 57% of the patients had abnormalities of left ventricular function and the cumulative dose of doxorubicin was the most significant predictor of abnormal function ($p<0.02$)[58].In a recent study of 6493 children who received anthracycline treatment, patients who received >550 mg/m^2 of anthracycline were five times more likely to have early cardiotoxicity than those who received lower cumulative doses [60].Despite a wide variation in patient sensitivity to anthracyclines, for most adults a total cumulative dose under 400-450 mg/m^2 is likely to result in chronic cardiotoxicity. To put the role anthracycline dosage in proper perspective, it is important to remember that a dose of anthracycline that does not result in late cardiac abnormalities has not been established. Altough cumulative doses in excess of 1000 mg/m^2 have been well tolerated by some patients [61,62], there are reports of cardiac dysfunction in patients treated with less than 300 mg/m^2[63,64]. No safe dose of anthracycline has been established .

3.2 Rate of anthracycline administration

There is evidence to suggest that the rate of anthracycline administration (continuous infusion versus bolus doses)has an effect on the relative risk of developing cardiotoxicity during or following treatment. This relative risk may differ significantly for adults & children. Lipshultz et al suggest that for pediatric patients ,even when the cumulative dose is limited, higher dose rates are an important predictor of impairment of left ventricular dysfunction years after treatment. Some investigators have suggested that anthracycline morbidity in adults can be reduced by use of prolonged intravenous infusions in place of bolus therapy[65,66].At equal doses .a longer time of infusion lowers the peak anthracycline blood level. In a survey of 1273 patients who had received doxorubicin, none of 182 patients who received slow infusions developed cardiomyopathy as compared to 2% of the patients who were treated with bolus doses [8]. In another study, a maximum single dose of >50 mg/m^2 was associated with a risk of cardiotoxicity 2.81 times greater than risk of cardiotoxicity associated with a lower dose [60].

However a recent study by Lipshultz et al showed cardiac Troponin T elevations in patients who received doxorubicin by either continuous or bolus infusion, suggesting that cardiac damage was not prevented by lower peak concentrations in continuous infusion [67].

3.3 Age

Children appear to be more vulnerable to anthracycline –induced myocardial impairment [68,69]. An age of <4 years at the time of exposure has been shown to be a risk factor for abnormal cardiac function ($p<0.003$)[58]. In another study of 120 children and adults who had received cumulative doses of 244-550 mg/m^2 of doxorubicin ,younger age at diagnosis was associated with and predictive of ventricular dysfunction

3.4 Length of follow up

With longer follow up after completion of anthracycline therapy, the prevalence and severity of cardiac abnormalities increase[70]. This is presumed to be related to the new cases of late - onset cardiac toxicity and worsening of previously detected early onset chronic progressive cardiomyopathy. The importance of longer follow up has only now become apparent, with the increasing numbers of asymptomatic cancer survivors at risk for cardiac dysfunction later in life.

3.5 Gender

Female patients appear to be vulnerable to the cardiotoxic effects of anthracyclines[60,71-74]. In a study of patients treated with anthracyclines, for childhood

cancers, female patients had significantly greater reduction in ventricular contractility, regardless of diagnosis. Similarly the higher the cumulative dose of anthracycline received, the greater was the difference in contractility between male and female patients. Altough the reason for this is not understood, differences in body composition between the two sexes may play a role by altering the distribution and metabolism of anthracycline[75,76]. Since girls have more body fat than boys for comparable body surface area and doxorubicin is reduced with increased body fat [77], equivalent doses of doxorubicin in girls could lead to higher concentrations, for a longer time, in non adipose tissue, including the heart

3.6 Concomitant mantle radiation

Radiation therapy is frequently used in combination with multidrug chemotherapy regimens in the treatment of patients with various hematologic cancers and solid tumors. Altough it is widely accepted that concomitant exposure of the mantle radiation and anthracycline enchances the risk of cardiotoxicity, the evidence, though suggestive is not conclusive. Proga et al evaluated the histologic features of endomyocardial biopsy specimens obtained from 12 patients who had received mediastinum radiation before anthracycline therapy and compared them with those of patients who had not received mediastinum radiation .They found a significantly higher severity of histopathologic changes in the patients pretreated with radiation ($p<0.01$).There are other reports in the literature that suggest radiation exposure enchances the cardiotoxic effects of

anthracyclines[78,79]. Most of these however remain anecdotal.

4 DETECTION & MONITORING

Long term cardiac monitoring performed locally for individual patient care but remeasured in a standardised manner is needed after exposure of any patient to anthracyclines. Cardiac risks and need for long term monitoring should be explained to patients before administration of anthracyclines. The education of primary care physicians, oncologists and cardiologists who care for survivors of childhood cancer regarding the late effects and their importance is essential to providing appropriate care to these patients.

A multidisciplinary approach with expertise in Oncology, Cardiology and quality of care, among others will be needed to understand true impact of cardiovascular abnormalities in long term survivors of cancer in childhood. Pregnant women, patients on growth hormones, competitive athletes may need closer monitoring, as many patients present with symptoms potentially cardiac in nature such as syncope, chest pain.

Many patients with mild to moderate left ventricular dysfunction may have no signs or symptoms of congestive cardiac failure and regular physical examinations are inadequate to detect anthracycline cardiotoxicity. However regular cardiac monitoring studies during treatment for cancer in paediatric patients may not necessarily predict

which patient will be at risk of developing late cardiac dysfunction [103]

4.1 Echocardiography

A complete echocardiography examination with two Dimensional, M mode and colour Doppler examination is the most commonly used method for examining ventricular function. Fractional shortening and ejection fraction are the most common indices used to assess left ventricular systolic functions. These indices are load dependent (104). Pre-load is the degree of diastolic filling of the ventricle. As the pre-load increases, the stroke volume and cardiac output increase. After-load is defined as the tension on the ventricular wall at the end of systole and is an indirect measure of the resistance the ventricle has to overcome to eject blood. Pre-load and after-load are frequently altered during chemotherapy and therefore need to be taken into consideration in the evaluation of each patient.

In general, echocardiography is a less invasive and more sensitive method of detecting abnormalities of left ventricular structure and function than other methods. In addition to providing anatomic details and measurements of chamber sizes and wall thickness, echocardiography enables the assessment of the relationship between the rate corrected velocity of fibre shortening and the end systolic wall stress, a reliable load independent measure of cardiac contractility that can be followed during and after anthracycline therapy[58].

4.2 Contrast radionuclide angiography:

In anthracycline induced cardiomyopathy, the left ventricular ejection fraction as measured with radionuclide angiography correlates with the severity of pathological changes seen on endomyocardial biopsy[105]. It has very good specificity (75%) for detecting patients at moderate to high risk of developing Congestive cardiac failure after anthracycline therapy. There are however some distinct limitations to this method. First, radionuclide angiography measures the ejection fraction which is a load dependent index of systolic function. In addition, it is a semi-invasive and moderately expensive procedure. The lack of a reproducible ejection fraction can lead to false-positive and false-negative results. Therefore, these studies should only be performed in well established, reliable nuclear medicine centres[65]. The usefulness of radionuclide radiographic measurement of left ventricular ejection fraction is often restricted to the older child or adult in whom echocardiographic windows are limited as in obesity or emphysema. The radiation exposure especially with repeated examinations, may be significant and may hinder its use for long term cardiac surveillance in some patients.

4.3 Endomyocardial Biopsy (EMB):

The value of EMB in assessing anthracycline cardiotoxicity has been questioned because the data is contradictory. In some studies, histologic examination of an EMB

specimen is a moderately sensitive test in adults for the effects of anthracyclines [106,107], shows a linear correlation with cardiotoxicity and is predictive of onset of early cardiac failure[108]. Yet, in other studies abnormailities were seen in biopsies of most patients who had received as little as 200 mg/m^2 of doxorubicin and the extent of abnormalities roughly correlated with the dose. However, the abnormalities were seen well before symptoms occurred and in fact were seen in many patients who did not develop symptoms after extended follow-up. In addition, other patients whose biopsy results were normal subsequently developed congestive heart failure [107].

EMB surveillance has many limitations. In addition to being invasive, it may involve a higher risk of complications in patients with cancer, who may already be at increased risk for excessive bleeding, infection and impaired wound healing [110]. Sampling error is highly possible as only the apical portion of the right ventricular septum is sampled. Since the left ventricle [65] is not sampled, the relevance of the results to left ventricular dysfunction may be limited. Currently, this method of monitoring is not feasible for many children or even for most adults.

4.4 Electrocardiogram:

The 12-lead electrocardiogram (ECG) is readily available and non-invasive. However, it lacks sensitivity for anthracycline related cardiotoxicity and does not measure LV function. It is useful for detecting ventricular hypertrophy and arrhythmias that may be seen in anthracycline cardiotoxicity. A study of 56 anthracycline treated long term

survivors of cancer suggested that prolonged QTc interval of the ECG may be useful in the timely detection of cardiotoxicity and progressive change in cardiac health. Even here, the changes are not specific for anthracycline induced cardiotoxicity. There is a very low correlation between ECG changes and the morphologic or clinical findings of anthracycline cardiomyopathy [111-113]

4.5 Chest X-ray:

Though familiar, non-invasive and readily available, the chest X-ray is not sensitive or specific and is usually not helpful in the early stages of anthracycline induced cardiomyopathy. In the late stages, after the onset of congestive heart faiure, non-specific cardiomegaly or pulmonary oedema may be apparent, as in congestive heart failure from any cause.

4.6 Biochemical markers of myocardial injury:

Biochemical markers may be useful for the detection of acute myocardial damage as a result of anthracycline therapy. A recent study evaluated cardiac troponin – T(cTnT) blood levels in 51 consecutive patients who received doxorubicin for ALL, cTnT elevations were observed[67]. These results suggest elevation of blood cardiac troponin T in children relates to the severity of myocardial damage. In addition, the magnitude of elevation in the anthracycline treated patients predicted left ventricular dilatation and wall thinning 9 months later, suggesting that serum cTnT elevations may predict

subsequent sub-clinical and clinical cardiac morbidity and mortality [67].

Measurement of cTnT is more sensitive than measurement of creatine kinase MB fraction for the assessment of acute anthracycline induced cardiotoxicity[67]. However, larger controlled trials are necessary to determine the sensitivity and applicability of these studies to the general adult and pediatric population.

5 TREATMENT

Despite the improved understanding of the changes occurring in the heart affected by anthracycline induced cardiotoxicity, appropriate rational therapeutic interventions remain difficult[12]. Current management modalities concentrate not only on symptomatic relief when symptoms occur, but also on correcting the underlying abnormalities, such as increased after-load and decreased contractility using after-load reducing and inotropic drugs.

5.1 After-load reduction:

After-load reduction with angiotensin converting enzyme inhibitors such as enalapril or captopril may be indicated in patients with elevated after-load and pre-clinical LV dysfunction diagnosed by echocardiogram. Although the consensus suggest that after-load reduction therapy should be initiated when after-load is elevated and contractility is impaired or when symptoms appear, there is not a proven role for preventive use of these medications, even when the patient is at apparently higher risk. With increased use

of these drugs in children, they appear to be effective and safe even in young children when used appropriately and with close monitoring. There are reports of short-term improvement after the use of enalapril in asymptomatic patients proven by echocardiography to have anthracycline induced dilated cardiomyopathy[115] but the results of prospective, randomized, placebo-controlled studies are currently lacking.

5.2 Management of heart failure:

Once symptoms of dysfunction occur, the decision to treat is easier. Treatment encompassing after-load reduction, diuresis and digoxin is standard for CCF, irrespective of the cause.

5.3 Transplantation:

With end-stage cardiac failure secondary to anthracycline induced cardiomyopathy, transplantation remains a viable option. For patients with significant restrictive cardiomyopathy, the failure to respond to diuretics, after-load reduction has resulted in the early listing for heart transplantation in this population to avoid the need for heart-lung transplantation. Reports suggest that treatment for cancer should not preclude cardiac transplantation when it is necessary[116,117]. The limited availability of donor hearts remains a problem for all patients awaiting organ transplantation.

6. PREVENTION

The primary goal in prevention, which is to identify the strategies that will maximize

oncologic efficacy while minimizing cardiac toxicities is not disputed. Validated strategies for detection and prevention of anthracycline induced cardiomyopathy however needs to be established. As the magnitude of the problem of cardiotoxicity in this patient population has become increasingly apparent over the last few years, the need for larger control studies to address this issue has become ever more urgent.

6.1 Limitation of cumulative dose:

The arbitrary magnitude of limitation of anthracycline dose is especially contentious and has been debated. To reiterate there is no safe dose of anthracycline at which no cardiotoxicity is seen. Therefore, reduction of cumulative anthracycline therapy is appropriate only when the minimized cumulative dose allows effective anti-tumor activity and the overall morbidity and mortality are reduced by this decision .Some authors have recommended a more cautious approach, with the anthracycline dose being reduced when any tests suggest cardiac injury [(118)]. This assumes that any abnormality or significant change in test results is due to anthracyclines. The available data do not justify adoption of this recommendation. Altough a reduction in anthracycline dose based on the sub clinical evidence of toxicity may seem reasonable, several factors must be considered .

- None of the methods of screening for anthracycline cardiotoxicity has been shown to be adequately predictive of early or late cardiac outcomes
- High cumulative doses of anthracyclines are intended to result in high cure rates

.If the reduction in anthracycline dose increases the death rate from cancer more than it decreases morbidity and mortality from heart failure, then patients will be ill served .Most patients would accept some impairment of cardiac function if the potential for oncologic cure were improved. Minor abnormalities of cardiac function would almost certainly represent an acceptable outcome, whereas disabling symptoms, early or late congestive heart failure or cardiac death would not.

- There are no adequately controlled, definitive studies demonstrating the efficacy of a dose reduction technique

6.2 Accounting for age and gender

Another preventive measure would account for age and sex in designing anthracycline treatment protocols. However, we must again employ caution and ensure that adequate doses of chemotherapy are provided for each patient. To do this properly, larger controlled trials are needed to provide appropriate guidelines for tailoring a chemotherapeutic regimen.

6.3 Continuous versus bolus infusion:

There is a suggestion that the use of prolonged intravenous infusions instead of bolus doses of anthracyclines may reduce the risk of cardiotoxicity, perhaps by lowering peak blood levels of anthracyclines[65,66]. Clinicians should be cautious when considering this

recommendation. The study discussed earlier, that showed an apparent reduction in the incidence of anthracycline-induced cardiomyopathy, was based on 182 patients, all adults, who received prolonged infusions[8]. In children with ongoing myocardial growth, concerns remain about potential risks of the longer anthracycline exposure period entailed in continuous infusions as a risk for less recovery of cardiomyocyte damage by anthracycline chemotherapy.

6.4 Cardioprotectants

Concurrent administration of cardioprotectants such as dexrazoxane and probucol has been suggested for prevention of anthracycline cardiotoxicity. Both dexrazoxane (ICRF 187) and probucol are antioxidants that are still investigated for their efficacy, limitations and potential risks.

6.4.1 Dexrazoxane

The specific mechanism of the cardioprotective effect of dextrazoxane is unknown[12]; it appears to prevent free radical formation[119-124]. Significant cardioprotection has been demonstrated in animal models[35], adult humans[36,37,39,40] and more recently, in small number of children[38]. It is currently approved for clinical use in women with metastatic breast cancer after a cumulative anthracycline dose of 300 mg/m^2.

Many questions remain to be answered about the efficacy and safety of dexrazoxane as a cardioprotectant. There is still a need for conclusive evidence that it reduces overall morbidity and mortality in children with cancer, as it is unclear whether the use of

dexrazoxane will be associated with reduced late-onset progressive cardiomyopathy. The mechanism of the potentially beneficial effects on the health of the myocardium is also unclear, and the effect of dexrazoxane on the response of most cancers to chemotherapy is currently unknown. There is some concern that dexrazoxane may interfere with the anti-tumour efficacy of anthracyclines[125]. In fact, lower response rates and faster anti-tumour progression times have been seen in patients with early breast cancer treated with dexrazoxane[21,126]. There is a concern that dexrazoxane may increase bone marrow depression, and both anthracyclines[127] and agents related to dexrazoxane[128] are potential risk factors for late recurrent or second malignancies.

6.5 Other strategies

Liposomal anthracyclines are now in phase II clinical trials, and the anthracycline structural analogs, such as mitoxantrone and idarubicin, which are known to be less cardiotoxic, have been considered as alternatives to anthracycline therapy. Their anti-tumour properties however appear to be less effective.

Beta-adrenergic blocking agents have been shown to reduce anthracycline induced cardiotoxicity[129] and prevent anthracycline induced intracellular calcium overload[130]. Calcium antagonist such as prenylamine have been studied for their efficacy in cardioprotection. While a pilot study suggested prenylamine may provide some cardioprotection in humans[131], animal studies have demonstrated both enhanced and reduced anthracycline cardiotoxicity with the use of calcium antagonist[129,132]. The use of

treatment such as intravenous immunoglobulins may reduce myocyte destruction and promote myocyte recovery[12].

7 CONCLUSION

Prevention of late cardiac dysfunction, especially late onset chronic progressive cardiomyopathy, is a priority for all patients and for their caregivers. Although many long term survivors of childhood cancer have asymptomatic persistent or progressive elevation of afterload with normal contractility 5-15 years after anthracycline chemotherapy, the real question remains what the condition of these patients will be in another 10, 20, 30, or more years[12]. We need protocol based cardiac follow-up of these patients to determine

1. Whether one protocol or intervention during treatment is better than another.
2. What the natural course of cardiotoxicity is.
3. What the risk factors for cardiotoxicity are.
4. Whether monitoring and dose modifications as currently practiced by some cancer centres improve survival.

Prevention is the future of minimizing anthracycline induced cardiotoxicity. It is important that all primary care providers be aware of the increasing numbers of asymptomatic cancer survivors at risk for cardiac dysfunction later in life. If the risk factors such as high cumulative doses of anthracycline treatment, young age the time of

exposure to anthracyclines, concurrent mediastinal radiotherapy, or any of the other risk factors introduced above are identified early, we may be able to minimize the adverse cardiac effects of anthracycline treatment.

SUBJECTS AND METHODS

All patients with a diagnosis of Non–Hodgkin's lymphoma or Hodgkin's lymphoma treated at Cancer Institute, Adyar, Chennai with atleast 5 years of follow up reporting to Out Patient Department were eligible. Patients had to be in complete remission after chemotherapy.

Inclusion criteria

1. Histological confirmation of lymphoma.
2. Baseline cardiac evaluation EF>50%
3. Last administration of anthracyclines at least 5 years back
4. Any age/gender.

Exclusion criteria

1. Non anthracycline based chemotherapy .
2. Active cardiac disease such as CHF or arrhythmias

After eligibility was determined, informed consent was obtained from all patients. Cardiac evaluation consisted of physical examination, Electrocardiogram, Chest x-ray and Echocardiography.

Echocardiographic Evaluation

Echocardiograms were analysed by a cardiologist who was unaware of each patient's treatment protocol, cumulative doses of anthracyclines, and potential risk factors. Each patient has been evaluated at least 5 years after the end of the last course of anthracycline by the cardiologist .The echocardiographic evaluation consisted of two Dimensional echocardiography and Doppler cardiography for the qualitative assessment of left ventricular regional wall motion, left ventricular end diastolic(LVED) and end systolic dimensions(LVES), ejection fraction(EF) were measured. Fractional Shortening (FS) was calculated with formula LVED-LVES/LVED. Echocardiography was considered abnormal if FS was below 25%, EF was below 50%, (measured in M-mode or by 2D echocardiography) and abnormal wall motion such as dyskinesis, hypokinesis, or akinesis were found.

Electrocardiographic Evaluation

The electrocardiogram (ECG) findings associated with anthracycline cardiac dysfunction include sinus tachycardia, low voltage, poor R wave progression, and non-specific T-wave changes. Even sinus tachycardia alone is a relatively late finding, such that serial ECGs are of little value in early detection [(135)].

CHARACTERISATION OF CLINICAL & SUBCLINICAL ANTHRACYCLINE-INDUCED CARDIOMYOPATHY [(134)]

Criteria	Clinical Cardiomyopathy	Subclinical Cardiomyopathy–

		decreased FS<25%
Clinical symptoms/ signs	Dyspnea on exertion Decreased exercise tolerance Tachycardia Pulmonary edema Hepatomegaly Gallop rhythms	Absence of clinical symptoms
Chest x-ray	Cardiomegaly Pulmonary edema Pleural effusions	No radiologic abnormalities
Echocardiography	LVEF 50 % accompanied with clinical symptoms	FS<25%
Negative signs	Absence of other causes of cardiomyopathy	Absence of other causes of cardiomyopathy

Statistical Analysis

The statistical analysis has explored the role of potential risk factors for the development of late cardiomyopathy. The role of each risk factor was studied by concomitant analysis of an FS lower than 25% which is the most reproducible parameter of left ventricular systolic function .

Seven variables were studied for their role in development of doxorubicin

cardiomyopathy: age, sex, cumulative doses of doxorubicin, mediastinal radiotherapy, diabetes, Hypertension and years of follow up.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Binomial proportion test has been used to find the significance of incidence cardiotoxicity in relation to the age, gender, follow up period and dose.

1. Z-test for a proportion (Binomial distribution)

Objective: To investigate the significance of the difference between the assumed proportion and the P0 and the observed proportion P

$$Z = \frac{(!p - p_0!) - 1/2n}{\sqrt{p_0 q_0 / n}}$$

2. 95% Confidence Interval

P ± 1.96* SE(P), Where SE(P) is the Standard error of proportion = P*Q/√n

3.Significant figures

+ Suggestive significance 0.05<P<0.10

* Moderately significant 0.01<P ≤ 0.05

** Strongly significant P≤0.01

Statistical software: The Statistical software namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc

RESULTS

Characteristics of 141 patients

Table 1: Age distribution according to gender

Age in years	Male		Female		Total	
	No	**%**	**No**	**%**	**No**	**%**
Up to 10	25	21.7	7	26.9	32	22.7
11-20	23	20.0	1	3.8	24	17.0
21-30	22	19.1	5	19.2	27	19.1
31-40	15	13.0	5	19.2	20	14.2
41-50	23	20.0	5	19.2	28	19.8
>50	7	6.1	3	11.5	10	7.1
Total	115	100.0	26	100.0	141	100.0
Mean ±SD	**27.30±16.72**		**29.12±18.55**		**27.64±17.02**	

Table 2: Distribution of lymphoma

Type of lymphoma	Number	%
Hodgkin's lymphoma	98	69.5
Non- Hodgkin's lymphoma	43	30.5
Total	141	100.0

Table 3: Adriamycin dose distribution(mg/m^2)

Adriamycin dose distribution(mg/m^2)	Number	%
101-150	4	2.8
151-200	11	7.8
201-250	53	37.6
251-300	67	47.5
>300	6	4.3
Total	141	100.0

Table 4: DM/Hypertension

DM/Hypertension	Number	%
DM	3	2.1
Hypertension	1	0.7
Total	141	100.0

Table 5: Follow up years

Follow up in years	Number	%
5-10	110	78.0
11-15	26	18.4
16-20	5	3.5
Total	141	100.0
Mean ± SD	**7.78±3.59**	

Table 6: Type of Chemotherapy

Chemo	Number	%
ABVD	24	17.0
CHOP	43	30.5
Hybrid	74	52.5
Total	141	100.0

Table 7: Cardio toxicity

Cardiotoxicity	Number	%
Absent	107	75.9
Present	**34**	**24.1**
Total	141	100.0

Table 8:Correlation between Age and cardiotoxicity

Age in years	Total number of patients	Number of patients with cardiotoxicity	% of patients with cardiotoxicity	P value
Up to 10	32	11	34.4	0.173
11-20	24	3	12.5	0.184
21-30	27	5	18.5	0.496
31-40	20	4	20.0	0.668
41-50	28	5	17.9	0.443
>50	**10**	**6**	**60.0**	**0.008****
Total	141	34	24.1	-

Table 9.:Correlation between Gender and cardiotoxicity

Gender	Total number of patients	Number of patients with cardiotoxicity	% of patients with cardiotoxicity	P value
Male	115	22	19.1	0.208
Female	**26**	**12**	**46.2**	**0.008****
Total	141	34	24.1	-

Table 10: Correlation between Type of Lymphoma & cardiotoxicity

Type of lymphoma	Total number of patients	Number of patients with cardiotoxicity	% of patients with cardiotoxicity	P value
Hodgkin's lymphoma	98	20	20.4	0.392
Non-Hodgkin's lymphoma	43	14	32.6	0.193

Table 11.: Correlation between Cumulative doses of Adriamycin and cardiotoxicity

Adriamycin dose (mg/m^2)	Total number of patients	Number of patients with cardiotoxicity	% of patients with cardiotoxicity	P value
101-150	4	0	0.0	-
151-200	11	3	27.3	0.804
201-250	53	8	15.1	0.126
251-300	67	18	26.9	0.592
>300	**6**	**5**	**83.3**	**<0.001****
Total	141	34	24.1	-

Table 12:Correlation between Years of follow up and cardiotoxicity

Follow up years	Total number of patients	Number of patients with cardiotoxicity	% of patients with cardiotoxicity	P value
5-10	110	21	19.1	0.220
11-15	26	8	30.8	0.424
16-20	**5**	**5**	**100.0**	**0.001****
Total	141	34	24.1	-

Table 13: Mediastinal Radiation and cardiotoxicity

RT site	Total number of patients (n=141)	Number of patients with cardiotoxicity (n=34)	% of patients with cardiotoxicity (24.1%)	P value
MEDIASTINUM	**15**	**8**	**53.3**	**0.053+**
CERVICAL	21	3	14.3	0.293

Figure 1:Adriamycin dose distribution

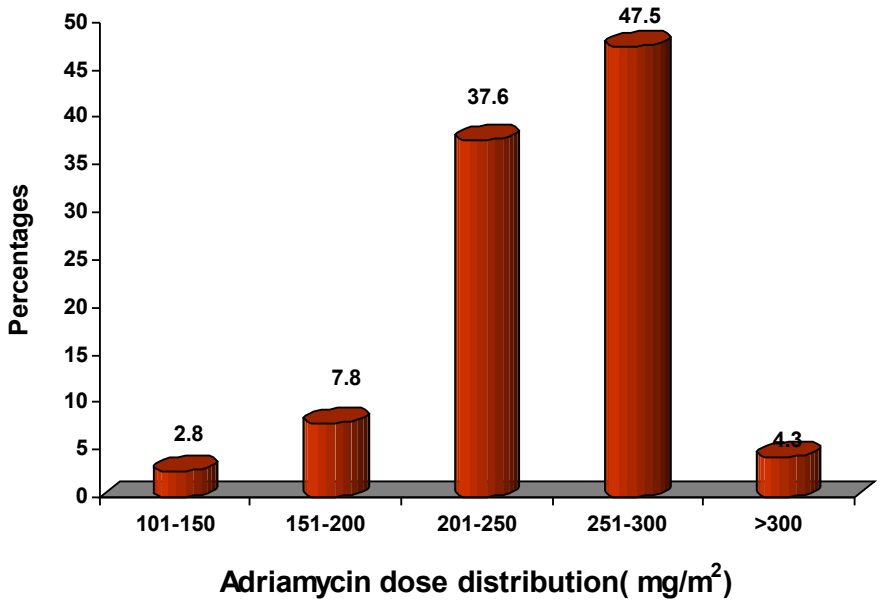


Figure 2:Cardiotoxicity

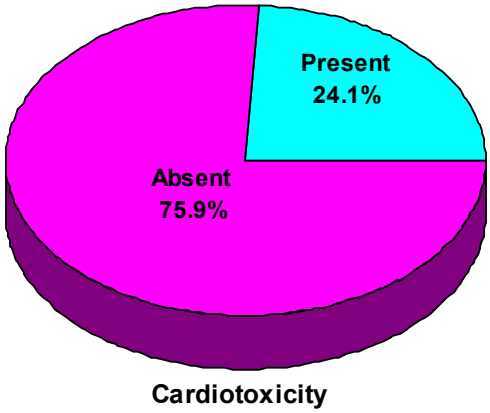


Figure 3:Correlation between Age and cardiotoxicity

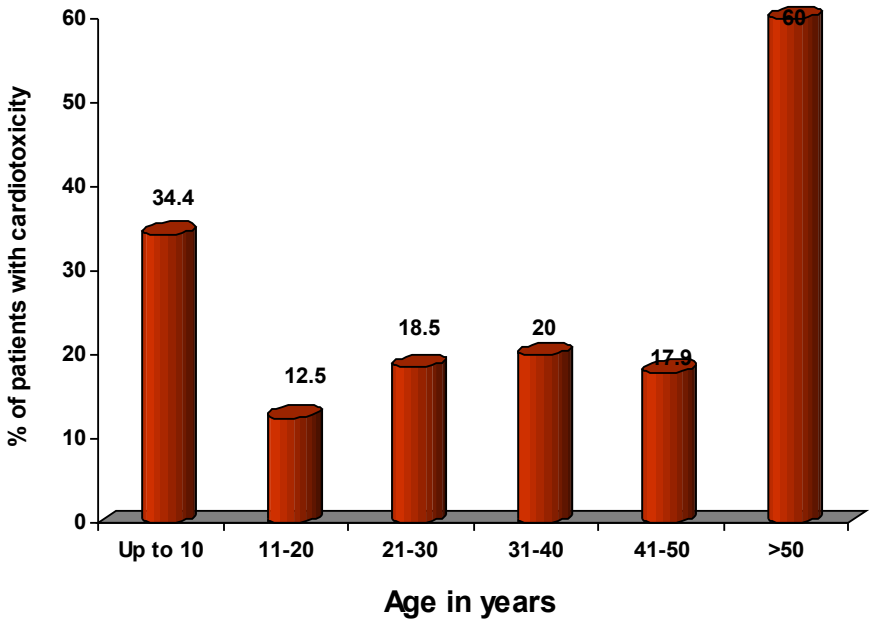


Figure 4:Correlation between Cumulative dose and cardiotoxicity

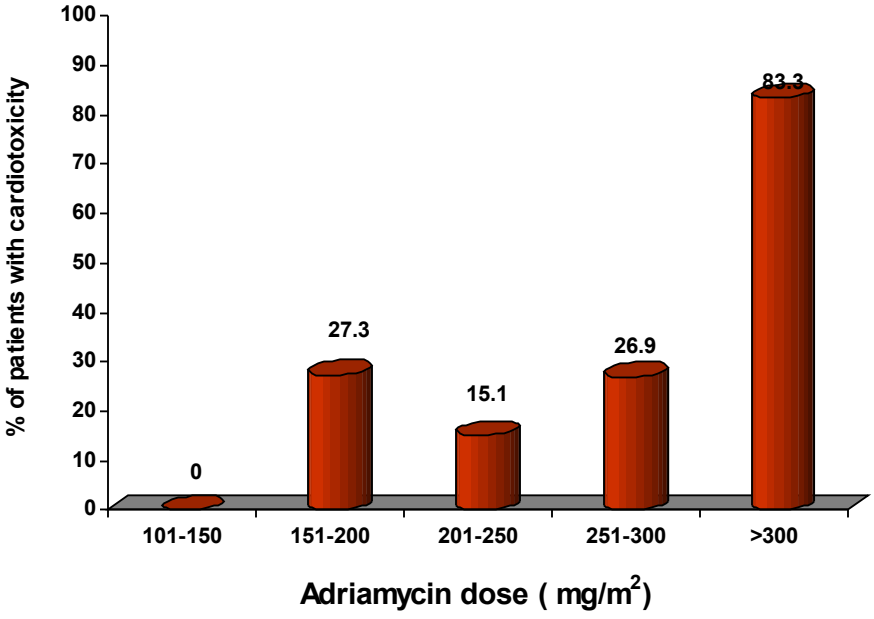


Figure 5:Correlation between Follow up and cardiotoxicity

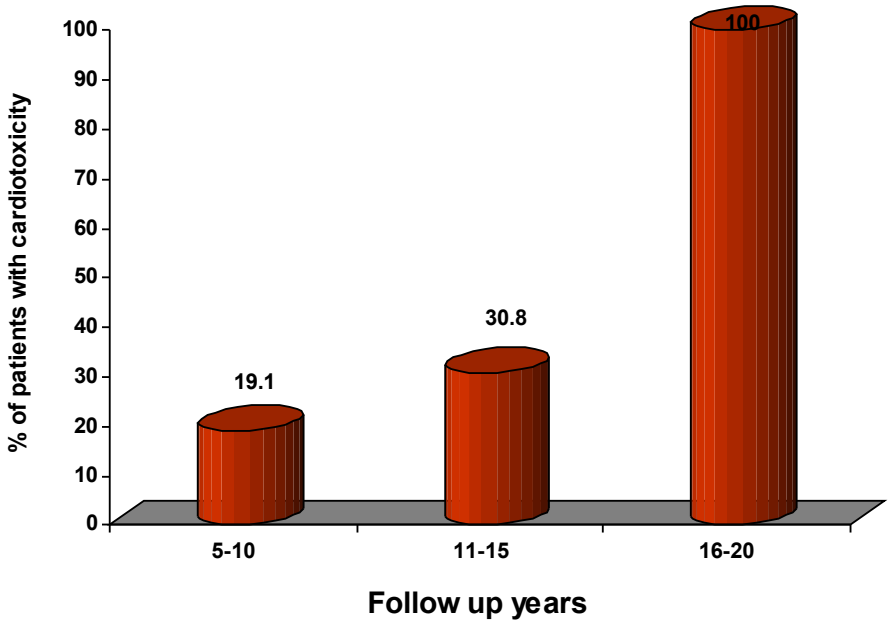
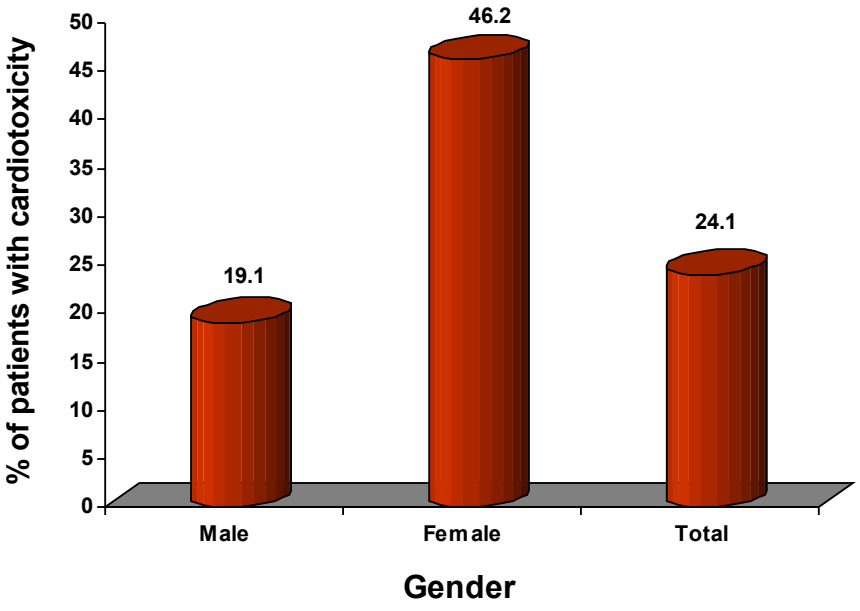


Figure 6: Correlation between Gender and cardiotoxicity



BASELINE CHARACTERISTICS

141 consecutive patients who came for follow up at Cancer Institute, Adyar Chennai met eligibility criteria for the study. All the patients had received their last dose of doxorubicin more than 5 years ago.

Patients were in age groups 4-69 years. Mean age at diagnosis was 27 years. Majority were in age group 0-20 years (Table 1).

Majority of patients were male who constituted 81.6% (n-115) (Table 1)

Majority of patients in the study were diagnosed as Hodgkin's Lymphoma constituted 69.5% (n-98).(Table 2)

The total dose of Adriamycin ranged from 100-410 mg/m^2. Majority of patients received adriamycin in range of 251-300 mg/m^2 who constituted 47.5% (n-67). 4.3% (n-6) patients received adriamycin dose of >300 mg/m^2. Of 6 patients who received >300 mg/ m^2, 5 patients received 400 mg/m2 and 1 patient received 410 mg/m^2. (Table 3) (Figure 1)

At the beginning of chemotherapy, 2.1 %(n-3) patients had Diabetes mellitus and 0.7% (n-1) had Hypertension (Table 4)

Mean duration between diagnosis and follow up cardiac evaluation was 7.7 years. (Table 5) (Figure 5)

Among all patients, 34 (24.1%) patients had cardiomyopathy. (Table 7) (Figure 2)

a. Clinical Cardiomyopathy

Of 34 patients with cardiomyopathy, only 2 (5.8%) patients had developed cardiomyopathy with dyspnea on exertion (grade 2) and congestive cardiac failure with follow up of 16 and 12 years respectively. Echocardiography confirmed the decreased ventricular function (EF-44% and 45%) with global hypokinesia.

b. Subclinical cardiomyopathy.

Doxorubicin –induced left cardiac dysfunction with decreased FS (<25%) was found in 32 (94%) patients. Cardiomyopathy was direct consequence of anthracycline treatment.

None of these patients had electrocardiography changes compatible with doxorubicin – induced cardiomyopathy (flattening of T wave, Prolongation of the QT interval, loss of voltage of R wave) or any clinical features of cardiomyopathy [(134)].

Analysis of risk factors and late cardiotoxicity

Older age appears to influence the development of left ventricular function .In this study patients above 50 years were prone for cardiotoxicity (p<008%). (Table 8) (figure 3)

Female gender showed correlation with cardiotoxicity with (p<0.008). (Table 9)

Significant correlation was seen between higher cumulative doses of anthracyclines and left ventricular dysfunction with ($p<001$). (Table 11) (Figure 4)

Risk of cardiotoxicity increased with increasing number of follow up ($p<0.001$). (Table 12). In our study patients with follow up of 16-20 had significant cardiotoxicity

Mediastinal Radiation along with adriamycin showed suggestive ($p<0.053$). (Table 13).Dose of anthracycline in patients with mediastinal radiation was between 210-300 mg/m^2. Radiation dose ranged from 3000-4000 cGy.

DISCUSSION

Echocardiography is the most widely used non-invasive evaluation of cardiac function and has been used largely to study anthracycline –induced cardiotoxicity, particularly in children.[17]. Primary parameters of systolic function are represented by measurements of Left ventricular ejection function(LVEF) and fractional shortening (FS); however measurement of LVEF is limited by a low sensitivity .Evaluation of FS has a higher sensitivity and specificity [18,19] and there after, had been chosen as the best index to assess systolic function after anthracycline treatment in routine monitoring[18].In children, FS below 28% or a decrease of 10 percentile compared with initial values are

criteria of systolic dysfunction [20,21]. Because few studies were performed in adults, specific criteria of anthracycline cardiomyopathy are not defined precisely. According to previous studies in asymptomatic left ventricular systolic dysfunction performed apart from the context of chemotherapy [22], we defined cardiomyopathy as a decrease of FS (<25%)and to increase specificity while preserving sensibility .we studied features of patients with decreased LVEF (<50%), decreased FS(25%) or abnormal function.

Among the 141 assessable survivors, 34 (24.1%) demonstrated decreased FS <25 %, Only 2 patients developed clinical symptoms of doxorubicin –induced CHF with ejection fraction 44-45 %. Thirty two patients demonstrated the presence of subclinical cardiomyopathy (FS<25%) .Evaluation of Fractional shortening has a higher sensitivity and specificity & has been chosen as the best index to assess systolic function after anthracycline treatment in routine monitoring [18].

Comparable rates of depressed contractility had been described in adult long –term survivors (range 14-37%) with a median cumulative doses of doxorubicin ranging from 200-350 mg/m^2[2,8,9,16].

In pediatric series of long –term survivors previously treated with comparable cumulative doses of doxorubicin ,the overall incidence of systolic abnormalities was similar [2,21,23].

Even if no cardiac treatment is required for asymptomatic patients,an appropriate follow up is recommended because evolution of these complications is not known. [24]

In our series, older age (>50 years) is a risk factor for development of doxorubicin – induced cardiomyopathy which was confirmed by previous studies [4,9,11] .

Female sex also predicts left ventricular dysfunction in our series. In study by O. Hequet et al[134], male sex was the major risk factor which predicted left ventricular dysfunction .

Patients with Diabetes Mellitus (DM) (n-3), Hypertension (HTN) (n-1) constituted 2.1% and 0.7% of assessable survivors respectively. As majority were young patients .Even at follow up, median age was 39 years . Patients at follow up did not have DM and HTN .So contribution of these comorbitities is unlikely.

In our study total cumulative doses of doxorubicin >300 mg/m^2 was associated with risk of cardiomyopathy.Total cumulative dose has been found regularly as a risk factor for development of cardiac dysfunction in previous studies in adults [4,7,9].

Length of follow up (5-16 years) is a risk factor of doxorubicin –induced cardiomyopathy in our study. Majority of the patients treated were young at the time of

diagnosis. So, it is important to have continued & prolonged follow up to know the incidence of cardiotoxicity. Steinherz et al[3] Thirty Eight percent of patients followed up for 10 years versus Eighteen percent of patients evaluated after less than 10 years had abnormal findings ..

In our series, only 15 patients received mediastinal radiotherapy with dose ranging from 3000-4000cGy & showed suggestive significance for doxorubicin –induced cardiomyopathy. Dose of adriamycin was between 210-300 mg/m^2 Previous radiotherapy to the mediastinum has been described as a risk factor [11,25]. Since cardiomyopathy in our study was seen in patients receiving anthracycline dose of >400 mg /m^2, mediastinal radiation has contributed to cardiac toxicity in our subset of patients who received doxorubicin dose in range of 210-300 mg/m^2.

Comparative studies

Parameter	**CIA(2008)**	**MSKCC-NY(1991)[3]**	**France(2003)[133]**
No of patients	141	201	141
Cardiotoxicity %	24.1%	23%	27.6%
Risk factors for late cardiotoxicity	Old age Female sex Total Cumulative	Total cumulative doses Length of	Male sex Old age Total cumulative doses

	doses Length of Follow up	follow up Mediastinal Radiation	Radiotherapy

Laurel J.Steinherz et al[3] analysed study in which 201 patients were evaluated by echocardiogram from 4-20 years after completion of anthracyclines with prospective and retrospective analysis .Twenty three percent (47/201)had abnormal cardiac function on non-invasive testing at long term follow up. Correlation between total cumulative dose ,length of follow up and mediastinal irradiation with incidence of abnormalities was significant. Fifty –six patients were followed up for 10 years or more (median 12 years), with a median anthracycline dose of 495 mg/m^2.Thirty eight percent (21/56) of these patients ,compared with 18% (26/145) of patients evaluated after less than 10 years had abnormal findings Sixty three percent of patients followed up to 10 years or more after receiving 500 mg/m^2 or more of anthracycline had abnormal findings. Nine of 201 patients had late symptoms, including cardiac failure and dysarrhythmia and three patients died suddenly.

O Hequet et al [133] analysed a group of patients (141) who previously received doxorubicin – based chemotherapy for lymphoma. Of 141 assessable patients, median age 54 years, median cumulative dose 300 mg/m^2, only one developed congestive heart failure. Criteria for subclinical cardiomyopathy were found in 39 patients. Risk factors that contributed to decreased FS were male sex, older age (>50 years), higher cumulative dose (>300 mg/m^2) and radiotherapy.

CONCLUSION

1. Cardiac abnormalities can occur in patients treated with doxorubicin for lymphoma in the absence of CHF, even who received moderate anthracycline doses (210-300 mg/m^2).

2. Older age (>50 yrs), female sex, higher cumulative dose of doxorubicin (>300 mg/m2), length of follow up (12-16 years). Mediastinal radiotherapy were risk factor for development of late anthracycline cardiomyopathy.

3. Significant incidence of abnormal cardiac function (24.1%) on long term follow up demonstrated by non invasive monitoring calls for continued follow up and appropriate evaluation.

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PROFORMA – HL/NHL

Name - **Age / Sex –** **s/no**

Date of Diagnosis –

Diagnosis - **Stage -** **IPI/IPSS –**

Symptoms

B symptoms	Y/N		
Chest pain	Y/N		
Abdomen pain	Y/N		
Bone pain	Y/N		
Head ache/seizures/FND	Y/N		

Comorbidities

HTN	Y/N	IHD	Y/N
DM	Y/N	others	Y/N

Signs

PS			
Bulky site	Y/N		
LNE	Y/N	if yes	C /A /I /Mediastinal /Abd
Hepatomegaly	Y/N		
Splenomegaly	Y/N		
Extranodal site		Y/N	if yes specify_____

Investigations

Hemogram	N/Abn	if Abn **specify** _____-
RFT	N/Abn	
LFT	N/Abn	
CECT chest/CXR	N/Abn	abn specify _____
CECT abd/USG	N/abd	Abn specify _____
ECG	N/Abn	Abn specify _____
Echo	N/Abn	
Abn specify	LVDD	
	LVSD _____	
	Chamber size _____	
	RWMA _____	
	Wall thinning _____	

EF%

Chemotherapy

Type – Hybrid/ABVD/CHOP/R-CHOP
No of cycles 4/6/8
Anthracycline cumulative dose –
Mode of anthracycline administration Bolus/IV
Concurrent cardiotoxic drugs Y/N

RT
Site – C/Ax/Inguinal/Mediastinal/Abdomen
Dose

Response evaluation
CR/PR/PD if PR specify _____
PD Specify _____

Relapse
HPE –
Stage –
DFS –
B symptoms Y/N
Salvage chemo Y/N
No of cycles

Response CR/PR/PD if PR specify _____
PD specify_____

Transplantation Indication
Conditioning regimen
Source of stem cells
Myelorecovery

Status at completion of Rx _____
Status at last F/U _____
Date of last F/U _____
No of yrs of F/U

Cardiac evaluation (5 yrs)
Symptoms Y/N
Signs Y/N
ECG
ECHO
MUGA

	Upfront	4 cycles	6 cycles	8 cycles	5yrs of F/U
ECG					

ECHO					
MUGA					