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Original Research Article

A STUDY ON EVALUATION OF ANTHRACYCLINE INDUCED CARDIOTOXICITY IN CHEMOTHERAPY PATIENTS IN A TERTIARY CARE HOSPITAL

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Abstract: A prime limiting factor in the administration of anthracyclines is cardiotoxicity. AIM : was to evaluate anthracycline induced cardiotoxicity among chemotherapy patients in a tertiary care hospital. **Materials and Methods:** A retrospective observational study was carried among patients treated with anthracyclines alone or in combination with other chemo drugs. One hundred and fifty patients were enrolled and data collection form was designed to collect data on social demographic characteristics, parameters like Type, Root and Duration of administration, Type of Regiment administered, Cardiac assessment of the patients before, during and after anthracycline chemotherapy, any reassessment done after sixth cycle of chemotherapy from patient medical records. **Results and Discussion:** Out of 150 patients 7 were found to be cardiotoxic (2 males and 5 females ($p<0.045$)), 6 patients of age above 51 were cardiotoxic ($p<0.025$). 2 patients (n=43) with 30 min duration of administration, 3 patient (n=71) with 1 hour duration, 2 patients (n=9) with 2 hour duration ($p<0.010$) were cardiotoxic. 1 patient (n=54) and 6 patients (n=96) were cardiotoxic after cycle 6 and cycle 8 respectively ($p<0.022$). 3 patients (n=28) of anthracycline and cyclophosphamide combination showed cardiotoxicity ($p<0.032$). **Conclusion:** Current study concludes that the prevalence of anthracycline induced cardiotoxicity was low due to close and strict monitoring of patients before, during and after each cycle of chemotherapy and even during the follow up which may extend up to several years.

Keywords: Anthracyclines, Cardiotoxicity, Age, Gender, Combination Therapy

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Introduction: Cancer is defined as a group of disease regarded as uncontrolled growth of cells. These cells will not react to the normal phase of cell cycle and cannot perform the normal physiological function of the normal differentiated counterpart. They possess the

capability to attack the adjacent normal tissue and metastasize and move through blood and lymph to institute new tumours at remote location. They also motivate the development of new blood vessels and their continuous duplication potential further add to their continued growth and survival.

Cancer can occur in any tissue of the body and can be categorized as benign and malignant[1]. Benign tumours are usually enclosed, localized, and idle. Malignant tumours attack the surrounding cells and spread to other locations, even though the primary tumour is eliminated. The cells no longer perform their normal functions, and their cellular manner changes. Anaplasia is termed as the loss of configuration and function. If malignant cells are allowed to grow uncontrollably, they can lead to the death of the patient[2].

Cancers usually spread by two pathways: through the bloodstream (haematogenous) or via lymphatics (evacuate through adjoining lymph nodes). The malignant cells that divide from the primary tumour discover suitable surroundings for growth. It is assumed that malignant cells produce mediators that encourage the development of blood vessels for growth and oxygen, the course of angiogenesis. The common metastatic locations for solid tumours are the brain, the bone, the lung, and the liver. It is significant to understand that breast cancer cells may spread to the brain, so the person may not have brain and breast cancer but breast cancer spread to the brain[2].

Signs and Symptoms

- Change in bowel or bladder habits.
- A wound that does not cure.
- Abnormal haemorrhage.
- Thickening or inflammation in breast or any part of the body.
- Upset stomach or difficulty in swallowing.
- Noticeable change in wart or mole.
- Irritating cough or roughness[2].

The principal properties of neoplastic cells includes

- ❖ The abnormal and self-sufficient growth signalling and insensitivity to anti-growth signals.
- ❖ Immortalization.
- ❖ Invasion and metastasis.
- ❖ Evasion of apoptosis.
- ❖ Sustained angiogenesis.
- ❖ DNA instability.

All the chemotherapeutic drugs act on the various phases of cell cycle. The entire cells display analogous cell division pattern with a little difference in the interval of cell cycle. The cell cycle is divided into various phases

- G_1 (Gap 1): A phase that leads to DNA synthesis.
- S (Synthesis) : A DNA synthesis phase
- G_2 (Gap 2): A time period following the cessation of DNA synthesis.
- M (Mitosis): The mitotic phase where the cell including double compliment of DNA divides into two daughter G_1cells.
- Each of these daughter cells either re-enter into cell cycle or into a non-proliferative stage,G_0(Gap 0).
- Usually G_0 cells of specific tissue may distinguish into functional cells and are incapable of division.
- Cells of the slow growing tumours remains in the G_0 phase for prolonged period of time and enter the cell cycle at a later phase[3].

Anthracyclines are one of the most commonly and widely used antineoplastic drugs. They were isolated from culture broth of pigment producing species of actinobacteria - *Streptomyces bacterium and Streptomyces peucetius*. These are used to cure many hemopoietic and solid cancers including ovarian, uterine, bladder cancer and breast, lung cancers, leukaemia, lymphomas. In childhood cancer, anthracyclines are incorporated in more than 50% regimens, contributing to a success level up to 75%[4].Daunorubicin with a trade name of Daunomycin was the first anthracycline discovered. Doxorubicin (Adriamycin) was developed soon

after, and other associated compounds were developed later.

Available agents include: Daunorubicin or Daunomycin, Doxorubicin or Adriamycin, Epirubicin, Idarubicin, Valrubicin– used in treatment of bladder cancer Mitoxantrone (analogue of anthracycline)[5]

Mechanism of Action: Anthracyclines act in four different mechanisms:

1. Hinder the DNA and RNA production by intercalation between base pairs of DNA/RNA strand; hence check the duplication of quickly increasing cancer cells.
2. Inhibiting topoisomerase II enzyme thus prevent the relaxation of supercoiled DNA and obstruct DNA transcription and replication.
3. It is presumed that topoisomerase II inhibitors help the topoisomerase II complex after the DNA chain has been broken down. This direct to topoisomerase II intervene DNA-cleavage, creating DNA breaks. The fastening of topoisomerase II inhibitor check DNA repair by ligase.
4. Iron-mediated production of free oxygen radicals that harm the DNA, proteins and cell membranes.
5. Initiation of histone expulsion from chromatin that relieve DNA damage response, epigenome andtranscriptome.[5]

Pharmacokinetics: Anthracyclines are administered intravenously and undergo complex hepatic metabolism and biliary excretion. Most of the anthracyclines have half-lives extending from 3-30hours while Idarubicin have a half-life of 15 hours and its active metabolite has 40 hours .All the anthracyclines are converted to an active alcohol intermediate and rapid uptake by heart, lungs, kidney, and spleen, liver. They do not cross blood-brain barrier[3].

Side Effects: Various toxicities of anthracyclines are bone marrow depression and cardiac toxicity. Cardiotoxicity defined as the decline of left ventricle ejection fraction (LVEF) larger than 10% of its normal limit of 50%.It is indicated by tachycardia, arrhythmia, pericardial effusion, hypotension, congestive heart failure, dyspnoea. Cardio toxicity from anthracyclines can occur at any point during and subsequent to treatment. This cardiac toxicity can be classified as acute, early and late effects.

Acute cardiotoxicity is usually seen during administration of drug or instantly after. It occurs in less than 1% of patients and is generally recognized by the presence of hypotension, tachycardia, arrhythmia, pericarditis and decreased myocardial contractility. Any kind of cardiac monitoring is not required during this stage. It is usually momentary and reversible.

Early cardiotoxicity is presented from few days to 12 months after administration. It is also known as Chronic Cardiotoxicity and is characterized by left ventricular dysfunction, chronic heart failure, and QT dispersion. It is distinctly dose dependent. Late cardiotoxicity, also known as Late Onset Cardiotoxicity develop after 12 months of administration and can extend up to many years after treatment. The occurrence of late-onset ventricular dysfunction appears to augment in combination with the duration of follow-up.

Other possible dangers associated with cardiac toxicity are

- Intravenous administration,
- Cumulative dose greater than 550mg/m^2,
- Female sex
- Former radiotherapy on the mediastinum,
- Combination therapy with other known cardiotoxic drugs,
- Age greater than 70,
- Pre-existing subclinical myocardial damage.
- Dose scheduling
- Hypertension
- Whole body hyperthermia[6].

Incidence of Cardiotoxicity:

1. The overall rate of drug induced chronic heart failure in patients receiving adriamycin is 2.2%.

2. The risk of developing cardiomyopathy increases with successive doses of drug as follows :

a. About 10% for those receiving between 550 and 600mg per sq.m.
b. About 30% for patients receiving more than 600mg per sq.m

Guidelines for Doxorubicin:

- Doxorubicin therapy should not be initiated with baseline LVEF 30%.
- In patients with LVEF>30% and<50% continuous studies should be obtained before each dose.
- Discontinue doxorubicin with cardiotoxicity: absolute decreases in LVEF 10 %(EF units) and or final LVEF 30%.
- Patients with known heart disease, ,exposure to radiation, ,abnormal ECG, cyclophosphamide therapy, or after 450mg/m^2 in the absence of any risk factors, perform sequential studies thereafter prior to each dose.
- Discontinue doxorubicin therapy are functional criteria for cardiotoxicity develop by absolute decrease in LVEF 10 %(EF units) associated with a decline to a level of 50% (EF units).

Detection and Monitoring of Cardiotoxicity

- Currently several methods are used for the detection and monitoring of chronic cardiotoxicity:
- ECG measurement
- Biochemical markers
- Determination of cardiac functional status
- Morphologic examination

Methodology: Aim: The aim of the study was to evaluate the anthracycline induced cardiotoxicity in chemotherapy patients in a tertiary care hospital.

Objectives:

- To determine the prevalence of anthracycline induced cardiotoxicity in patients at KMCH Hospital.
- To determine the rate of anthracycline induced cardiotoxicity based on gender and age.
- To compare the incidence of anthracycline induced cardiotoxicity based on duration of administration of medicine.
- To compare the incidence of anthracycline induced cardiotoxicity among different chemotherapy regimen.

Study Design: It is a retrospective study conducted in chemotherapy patients who were treated with anthracyclines.

Study Site: The study was conducted in the Department of Oncology, Kovai Medical Center and Hospital, a super specialty hospital in Coimbatore, Tamil Nadu. The study was approved by the Ethics committee of the Hospital.

Study Period: The study was conducted from November 2014 to July 2015.

Study Population:

A total of 150 patients were included in this study.

Study Criteria:

Inclusion Criteria: All the patients who had undergone anthracycline chemotherapy.

Exclusion Criteria:

- Patients whose Ejection Fraction<50%.
- Patients having history of cardiac problems.

Sources of Data:

- Patient's case reports
- Treatment charts.

Study Protocol: Patients who undergone the anthracycline therapy during the year 2013-2015were selected for the study. From those, 150 patients who met the inclusion criteria were selected for the study. Data of patients including demographics, disease, types of regimen, dose, route and duration of administration, the cardiac assessment of the patients before, during and after the treatment is collected from ECG, Echocardiogram and patient case files.

Statistical Analysis: Data was analysed with the aid of Microsoft Office Excel 2010 and SPSS 20.0 version. Statistical analysis was performed by applying Pearson's Chi-square test. Results were considered significant when $p<0.05$.

Results: This retrospective study evaluates the cardiotoxicity induced by anthracycline in cancer patients. A total of 150 patients were included in the study. It was conducted in a period of November 2014 to July 2015.

For the study, the registers in the medical record department had been thoroughly searched and a list of patients who had undergone anthracycline therapy was made. From this a list of 150 patients was made whose complete details were available. A documentation sheet was maintained comprised of Register number ,Name, Age, Sex, Height, Body weight, Body Surface Area, Type of cancer, Type of regimen, Route of infusion, Type of infusion, Duration of infusion, Number of cycles, Reassessment done or not ,Cardiac assessment and its impression by the cardiologist.

Data Entry Form: In this study, the total population was classified into normal and abnormal where normal denotes those patients without any cardiotoxicity after anthracycline treatment while abnormal denotes those patients with cardiotoxicity after treatment. Out of 150 patients 49males and 94 females were normal while 2 males and 5 females were found to be abnormal (Table 1, Figure 1). The p value 0.045obtained from Chi square test was shown to be significant.

The total study population was classified on the basis of chemotherapy regimen. The various regimens are RCHOP, AC, ABVD, EC, CHOP, and EOX. RCHOP is the acronym for Rituximab, Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisolone while CHOP stands for Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisolone.AC includes Adriamycin and Cyclophosphamide, ABVD is the combination of Adriamycin, Bleomycin, Vinblastine, Dacarbazine while EC includes Epirubicin, Cyclophosphamide and EOX is Epirubicin, Oxaliplatin. Of the 18 patients who received RCHOP, 17 patients were found to be normal and 1 was found to be abnormal. Out of 83 patients who received ABVD, 80 patients were found to be normal and 3 were found to be abnormal. Among 31 patients who received AC, 28 patients were found to be normal and 3 were found to be abnormal. No cardiotoxicity was reported among 11 patients who received EC, 2 CHOP recipients and 5 EOX recipients (Table 2, Figure 2).The p value 0.032 was observed as significant.

The total study population (150 patients) was classified on the basis of cycles of chemotherapy they had undergone. Out of 54 patients who completed therapy at cycle 6, 53 patients were found to be normal and 1 was found to be abnormal. From the 96 patients who completed treatment at cycle 8, 90 patients were found to be normal and 6 were found to be abnormal (Table 3, Figure 3).The p value 0.022 was obtained by the chi square was found to be significant.

The patients enrolled in the study were classified into two groups on the basis of age. Out of 83 patients in the age group of 50 years and below, 82 were found to be normal and 1 was abnormal. Among 67 patients in the age group of 51 and above, 61 patients were found to be normal and 6 were found to be abnormal (Table 4, Figure 4).The p value 0.025 obtained from chi square test was found to be significant.

The study population was classified on the basis of duration of administration. No cardiotoxicity had reported among 17 patients who had 20 minute administration and 10 patients who had 3 hour administration. Among 43 patients who had 30 minutes administration, 41 patients were normal and 2 patients were abnormal. Among the 71 patients who undergone 1 hour administration, 68 were found to be normal and 3 were found to be abnormal. From the 9 patients who had 2 hour administration, 7 were found to be normal and 2 were found to be abnormal(Table 5, Figure 5).The p value 0.010 obtained was significant.

The study population was evaluated for cardiotoxicity in three stages of treatment that is before treatment, during and after treatment. All

the 150 patients were found to be normal before the treatment (Table6, Figure 6). The entire population was found to be normal during the treatment (Table 7, Figure 7). After completion of treatment, 143 patients were found to be normal and 7 patients were found to be abnormal (Table 8, Figure 8).

Based on type of infusion, 150 patients were classified into two categories-central and peripheral. Among this, 7 patients (4.7%) were centrally infused while 143 patients (95.3%) were peripherally infused (Table9, Figure 9).

The total population was distributed based on route of infusion. Five patients (3.3%) had intravenous bolus and 145 patients (96.7%) had intravenous infusion (Table10, Figure10).

In an overall view, the prevalence of anthracycline induced cardiotoxicity is less among the patients due to strict monitoring of cardiac status before, during and after the therapy.

Tables and Graphs

Table 1: Gender Wise Classification of Total Population.

S. No	Cardiotoxicity	male	female	p Value
1	Normal	49	94	0.045*
2	Abnormal	2	5	

* $p < 0.05$ is significant.

Figure 1: Gender Wise Classification of Total Population.

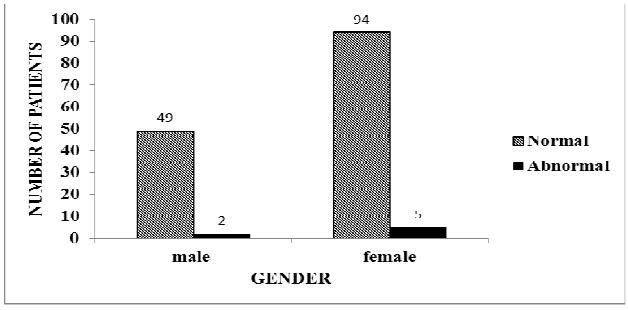
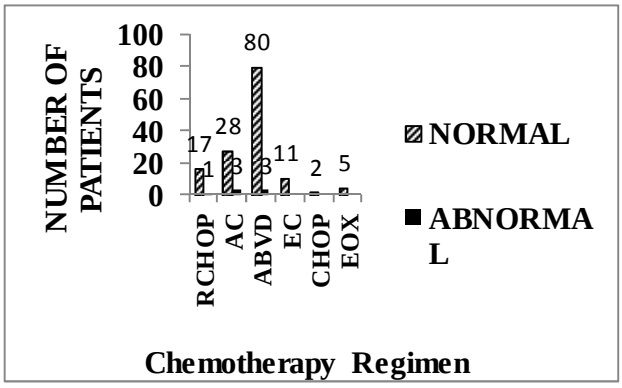


Table 2: Classification of Patients Based on Chemotherapy Regimen.

SL NO	Regimen	Normal	Abnormal	p Value
1	RCHOP	17	1	0.032*
2	AC	28	3	
3	ABVD	80	3	
4	EC	11	0	
5	CHOP	2	0	
6	EOX	5	0	

* $p < 0.05$ is significant.

Figure 2: Classification of Patients Based on Chemotherapy Regimen.



AC: Adriamycin, Cyclophosphamide
ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine.
EC: Epirubicin, Cyclophosphamide
EOX: Epirubicin, Oxaliplatin
CHOP: Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisolone
RCHOP: Rituximab, Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisolone

Table 3: Classification of Total Population Based on Cycles of Therapy.

S. No	Cycles	Normal	Abnormal	p Value
1	cycle 6	53	1	0.02*
2	cycle 8	90	6	

* $p < 0.05$ is significant.

Figure 3: Classification of Total Population Based on Cycles of Therapy.

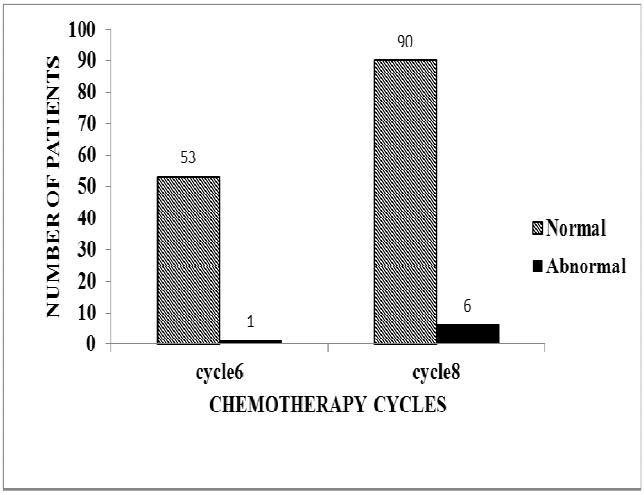


Table 4: Age Wise Classification of Total Population.

SL No	Age	Normal	Abnormal	p Value
1	≤50	82	1	0.025*
2	>51	61	6	

* p <0.05 is significant.

Figure 4: Age Wise Classification of Total Population

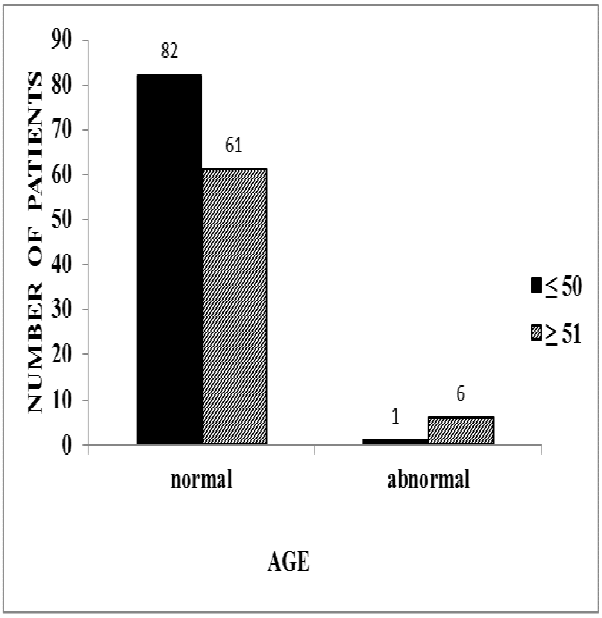


Table 5: Duration of Administration.

SL No	Time	Normal	Abnormal	p Value
1	20 min	17	0	0.010*
2	30 min	41	2	
3	1hour	68	3	
4	2hour	7	2	
5	3hour	10	0	

* p <0.05 is significant.

Figure 5: Duration of Administration.

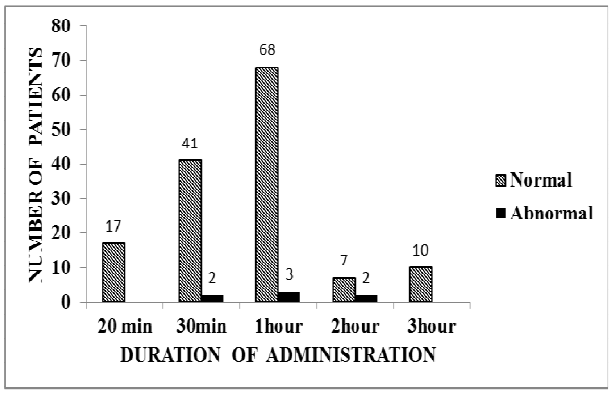


Table 6: Distribution of Cardiotoxicty among Total Population before Treatment.

SL No	Cardiac Status	Number of Patients	Percentage
1	Normal	150	100
2	Abnormal	0	0

Figure 6: Distribution of Cardiotoxicty among Total Population before Treatment.

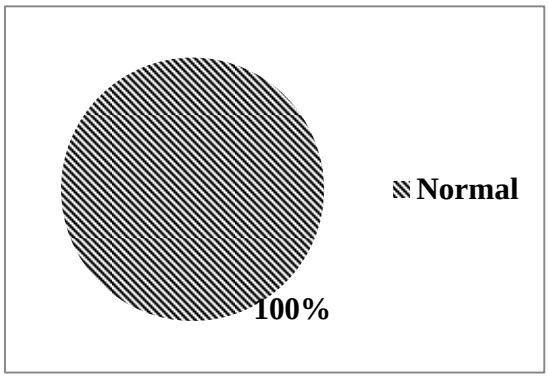


Table 7: Distribution of Cardiotoxicty among Total Population during Treatment.

SL NO	Cardiac Status	Number of Patients	Percentage
1	Normal	143	95.3
2	Abnormal	7	4.7

Figure 7: Distribution of Cardiotoxicty among Total Population during Treatment.

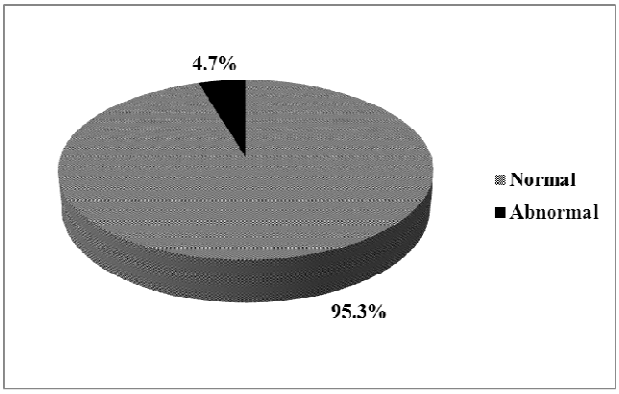


Table 8: Distribution of Cardiotoxicty among Total Population after Treatment.

Sl No	Type	Number OF Patients	Percentage
1	Central	7	4.7
2	Peripheral	143	95.3

Figure 8: Distribution of Cardiotoxicty among Total Population.

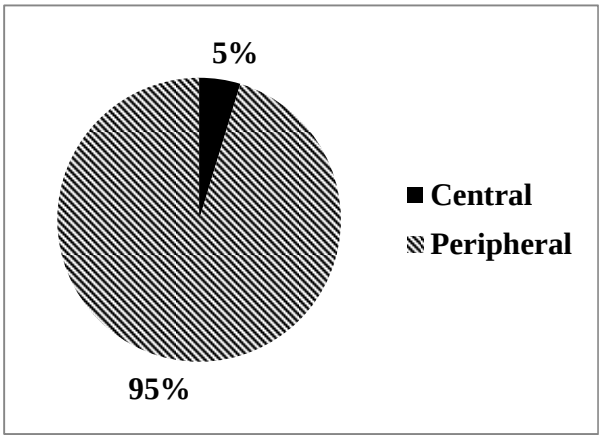


Table 9: Distribution of Total Population Based On Type of Infusion

SL NO	Cardiac Status	Number Of Patients	percentage
1	Normal	150	100
2	Abnormal	0	0

Figure 9: Distribution of Total Population Based on Type of Infusion.

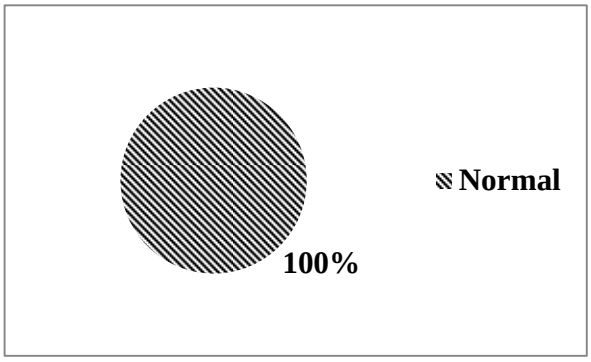
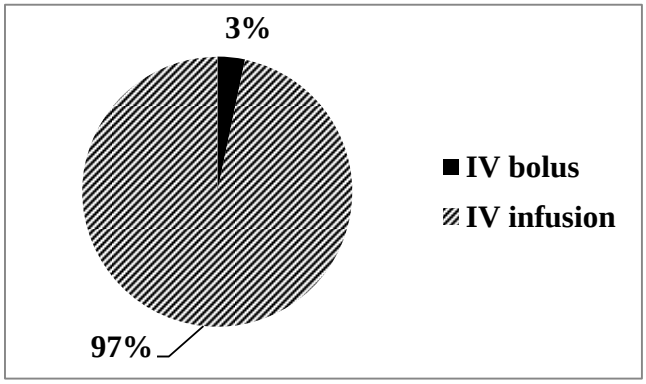


Table 10: Distribution of Total Population Based On Route of Infusion.

Sl No	Route	Number of Patients	Percentage
1	IV bolus	5	3.3
2	IV infusion	145	96.7

Figure 10: Distribution of Total Population Based on Route of Infusion.



Discussion: Anthracycline antibiotics have been widely used as chemotherapeutic drugs against a range of cancers. Dose-dependent cardiotoxicity had been reported where age, gender, pre-existing heart disease, hypertension, and mediastinal irradiation are implicated as contributing factors to the development of doxorubicin associated cardiomyopathy. [7]

In this study, the significance of gender in anthracycline induced cardiotoxicity was evaluated. It was found that females were more susceptible which was contradictory to results of many studies. Our result was supported by the study carried out by Steven et *al* [23] where they concluded that differences in the body composition between males and females could influence drug toxicity by changing the metabolism or the volume of distribution of doxorubicin. It does not reach a higher concentration in fat and its clearance is reduced with increased body fat. Hence even if patients have same body surface area, equivalent doses of doxorubicin could lead to higher concentrations for a longer time, in non-adipose tissue (including heart) in females.

In the current study, the patients were grouped above and below 50 years and found that patients above 51 years were more susceptible to anthracycline induced cardiotoxicity. A similar study was done by Geoffrey *et al*[6] where the limit was set above 45 and below 45 years in which patients above 45 years were more susceptible to cardiotoxicity.

In the study population, various chemotherapy regimens like RCHOP, CHOP, EC, AC, EOX, and ABVD were given. Among these, AC has shown higher rates of cardiotoxic cases which is supported by Sandra *et al*[23] whose study concluded that synergistic cardiotoxicity of anthracycline antibiotics together with other cytostatic is probably related to the accumulation of toxic effects within myocardium. Hence continuous monitoring of doses of other drugs in combination with anthracycline therapy is essential.

Higher rate of cardiotoxicity was found in patients who had undergone two hour continuous infusion. Similar study done by Van *et al*[24]concluded that anthracycline infusion duration of six hours or longer reduced the risk of clinical heart failure where no difference in response rates was observed.

Cardiac events were defined as one of three changes in Left Ventricular Ejection Fraction values (LVEF) compared with baseline value which was taken prior to the treatment. Even though no abnormal cardiac events were reported during the treatment, 7 patients were found cardiotoxic during follow-up. In our study, the impression given by the cardiologist after checking ECG or Echocardiogram of the patient was more reliable than the values to conclude the cardiac status. Recording of cardiotoxicity by LVEF for years after anthracycline administration is much more meaningful end point because no considerable change in systolic function occurs until a critical amount of morphological damage has been taken place. These results were congruent with the study results of Tjeerdsma *et al*[25].

Conclusion: Anthracyclines are chemotherapeutic agents which are highly effective against a wide range of neoplasms. A prime limiting factor to the administration of this drug is cardiotoxicity, which commonly develops when the cumulative dose exceeds 500 mg/sq.m. When anthracyclines (AC), either used alone, or in combination with other chemotherapy agents. AC-induced injury has been described as “type I” cardiotoxicity which is dose-dependent, progressive, and generally irreversible type of toxicity.

This study indicates that the age above 51and females are more susceptible to cardiotoxicity due to anthracycline.

Left ventricular ejection fraction (LVEF) is a commonly accepted measure of cardiac systolic function and is accepted as an indicator of prognosis. In this study LVEF and other echocardiograph variables are assessed before,

during and after treatment and the statement by the cardiologist confirms the cardiac status.

Increased frequency of cardiovascular complications and cardiotoxicity is found in relatively small cumulative doses of anthracycline antibiotics when they are administered along with cyclophosphamide. Synergistic cardiotoxicity of anthracycline antibiotics together with other cytostatic drugs is probably related to the accumulation of toxic effects within myocardium. Hence monitoring of doses of other drugs in combination with anthracycline therapy is important.

The method of anthracycline administration influences the risk of permanent cardiovascular system damage with an increased drug concentration in serum due to short term intravenous infusion.

In the present study, the patients with anthracycline induced cardiotoxicity were found to be limited in number. It is due to the close monitoring of patients of patients after each cycle of chemotherapy. Monitoring includes the patient interview or enquiry regarding the clinical and subclinical symptoms. In case of any suspicion, he/she will be assisted to the cardiology department for detailed examination using ECG and Echocardiogram .If any abnormality is detected, patient will be treated with cardiac drugs or whole treatment pattern including chemotherapy regimen or dose or dosing schedule will be altered. Even if no suspicion was observed during treatment, patient will be subjected for reassessment of cardiac status and total health after cycle 6 of chemotherapy. This monitoring is done even during the follow-up carried out in the consecutive years.

As the number of patients in anthracycline chemotherapy was limited various parameters like types of infusion and mode of administration cannot be assessed. An extensive study can be conducted with large population either in the same study centre or at multiple centers. A prospective study is more reliable pattern to acquire detailed information of each patient so that the relationship with different factors and anthracycline induced cardiotoxicity can be assessed.

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