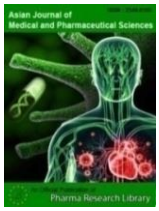

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A Retrospective & Prospective Observational Study on Cardiac Dysfunction by Anti- Cancer Drugs (Chemotherapy & Immunotherapy)

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A b s t r a c t

Introduction: Cancer therapy-related cardiac dysfunction (CTRCD) is one of the most feared and undesirable side effects of chemotherapy, occurring in approximately 10% of the patients. Cardio-oncology is an uprising field that has transformed the medical management of patients with cancer. It incorporates the prevention and treatment of cardiovascular dysfunctions related to cancer treatments, aiming to reduce cardiac adverse events among cancer survivors.Aim & Objectives: The aim of our study was to determine the incidence of CD by chemotherapy and immunotherapy and to evaluate echocardiographic and biomarker changes during the therapy.Methodology: It is a retrospective and prospective observational study conducted for a period of 6 months in a tertiary care hospital. The data was collected from the 55 patients with cancer who underwent treatment with doxorubicin, trastuzumab, pembrolizumab and nivolumab after approval of the protocol by the IEC of Medicover Hospitals. The statistical analysis was done by using SPSS software, V.22. (1) 1. SPSS I. IBM SPSS Statistics Version 22 Statistical Software: Core System Users' Guide. SPSS Inc. 2014.Results and discussion: Majority of CD patients were females (75%) compared to men (25%) and most of them were advanced age >55years. The incidence of CD was found to be 12.5% with the administration of doxorubicin and trastuzumab. Most of the patients with CD were reported to have a past medical history of HTN i.e., 7 (87.5%) which is statistically significant ($p < 0.05$). Few CD patients were reported to have a family history of cardiac disease, past history of DM, smoking which are clinically significant but statistically insignificant ($p > 0.05$). A significant reduction in EF and GLS is seen in CD patients from 0-3 months and from 0-6months who are administered with doxorubicin and trastuzumab ($p < 0.05$). CD patients who are administered with pembrolizumab had a statistically significant reduction in EF and GLS from baseline to 6months ($p < 0.05$). Conclusion: The study concludes that patients administrated with chemotherapeutic drugs like Doxorubicin and Trastuzumab have a higher probability to develop CD than patients who are administrated with immunotherapeutic drugs such as Pembrolizumab and Nivolumab with an incidence of 12.5%. The incidence is seen more in patients that have co-existing conditions such as HTN & DM with females being more prone to it. GLS can be a useful and critical parameter in monitoring early CD in cancer patients. Careful monitoring is required during the treatment.

Keywords: Pembrolizumab, Nivolumab, doxorubicin, trastuzumab, CTRCD

A r t i c l e I n f o

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C o n t e n t s

1. Introduction

Cancer is the uncontrolled growth of abnormal cells in any part of the body. These abnormal cells are termed either as cancer cells, malignant cells, or tumour cells. These cells can infiltrate normal body tissues. Many cancers and the abnormal cells that compose the cancer tissue are identified by the name of the tissue that the abnormal cells have originated from (for example, breast cancer, lung cancer, colorectal cancer).

Chemotherapy:

Chemotherapy is basically used to control the disseminated subclinical disease and, for elementary lesion treatment; moreover, this method could be followed by other modalities. For preventing drug resistance, different drug classes and modes of action are used in chemotherapy. The purpose of cytotoxic chemotherapy is to eradicate tumor cells while sparing normal tissue, the sensitivity of tumors varies by histology and class of drugs with high cure rates in tumours that are highly sensitive to the drug administrate.[6]

Radiotherapy:

Treatment of invasive cancer by radiotherapy consists of ionization radiation that delivers a lethal dose to a defined tumor volume. Therefore, radiation will damage the DNA, and cancer cells will die especially when the cells attempt mitosis with the minimum possible damage to surrounding normal tissues. [6] Radiation therapy side effects can depend on the type of cancer, its location, the radiation therapy dose, your general health, and other factors. Depending on the type and location of where radiation therapy is directed at the body.

Surgery:

Cancer surgery attempts to completely remove localized tumors or reduce the size of large tumors so that follow-up treatment by radiation or chemotherapy will be more effective. It is the oldest form of treatment for cancer. Other than its curative purpose, cancer surgery may be done as a diagnostic (staging) process or a preventive measure. Surgeries are also performed to relieve pain or repair deformities and abnormalities caused by surgical treatment for cancer. [9]

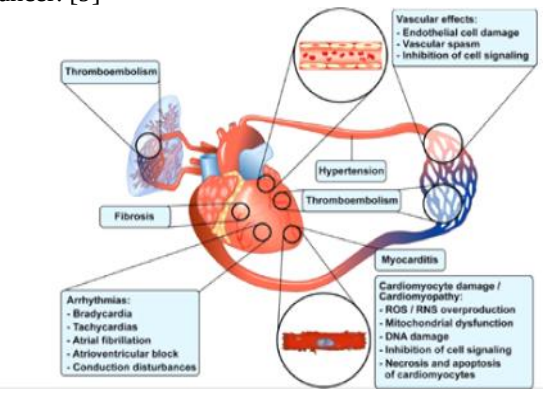

Fig.1: Schematic representation of some of the cardiovascular dysfunction associated with antineoplastic drugs in patients with cancer.

Targeted therapy:

Drugs which are used in systematic chemotherapy have targeted the dividing normal and tumor cells. Therefore, newer techniques were needed to reduce the disadvantages of chemotherapy. Targeted therapy utilizes drugs that have less severe side effects and only tumor cells are affected by drugs. Monoclonal antibodies and small molecule inhibitors are the two main types of targeted therapy. In these techniques tumor growth is stopped by barricading the biochemical pathway or function of proteins which have the crucial effect on proliferation and survival of tumor cells. [6]

Immunotherapy:

Immunotherapy is treatment that uses a person's own immune system to fight cancer. Immunotherapy can boost or change how the immune system works so it can find and attack cancer cells. [11]

Mechanism of doxorubicin induced Cardiac dysfunction:

Oxidative stress

Production of free radicals is the primary concern that produces cardiac muscle cell injuries after Dox administration. Dox-induced cardiotoxicity appears via increased ROS production and lipid peroxidation in cardiac tissues. These mechanisms have shown the involvement of various enzymes like NOS (nitric oxide synthase), NADPH oxidase (NOX), mitochondrial-dependent ROS production and many more, which activates oxidative stress.

NOS dependent increased ROS production

Doxorubicin binds to the eNOS (endothelial nitric oxide synthase) reductase enzyme and induces Doxsemiquinone radical formation, which reduces the free oxygen into the superoxide (O2--) free radical, leading to cardiotoxicity. Antisense eNOS mRNA reduces the stimulation of the caspase-3 activity, indicating the cardioprotective effect over Dox-induced cardiotoxicity. There are three types of NOS (nitric oxide synthase) in our system: eNOS, i (inducible) NOS, and n (neuronal) NOS. Dox administration increases the iNOS transcription and protein expression and induces the formation of nitrotyrosine (NT) with increased mitochondrial superoxide level in cardiac tissue, which causes apoptosis of the cardiac muscle cells, decreased cardiac contractility, and decreased CAT and glutathione peroxidase activity.

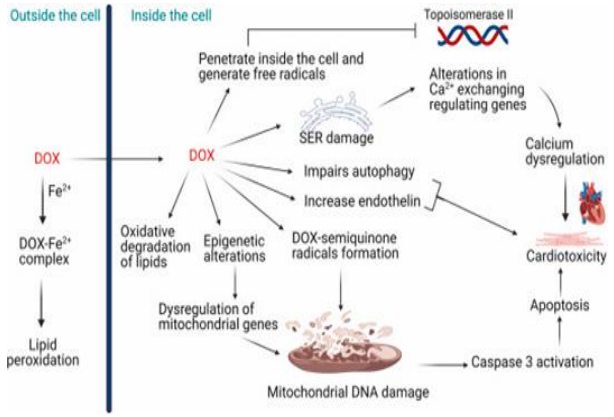

Fig.2: Schematic representation of different mechanisms of action of Dox-induced CD inside the cell and outside the cell.

Mechanism of Trastuzumab induced Cardiac Dysfunction: Trastuzumabdownregulates neuregulin-1 (NRG-1), which is essential for the activation of cell survival pathways in cardiomyocytes and the maintenance of cardiac function. NRG-1 activates the MAPK pathway and the PI3K/AKT pathway, suppression of cell survival via the Src/Fak pathway, and upregulation of protein degradation via FOXO signalling. These are all significant for the function and structure of cardiomyocytes. Trastuzumab can therefore lead to cardiac dysfunction. [43]

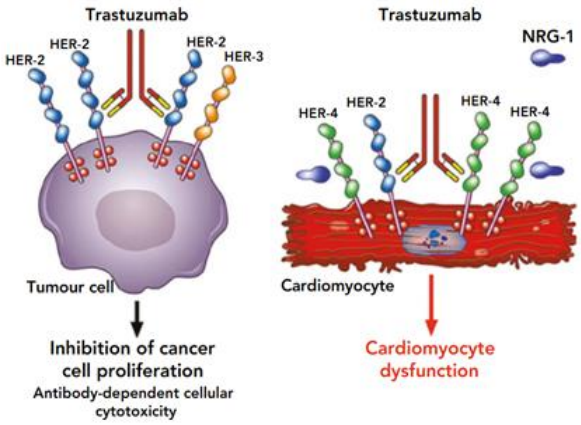

Fig.3: Schematic representation of Mechanism of Action of Trastuzumab and Pathogenesis of its CD

Mechanism of ICI mediated CD:

Both cancer cells and cardiomyocytes express PD-L1, ICIs bind to cancer cells and as well as to non-target cardiomyocytes. ICIs bind to cardiomyocytes and modulates immune function and promote muscle inflammation (autoimmune myocarditis) in heart muscle. Additionally, ICIs can induce left ventricular hypertrophy and cause cardiac dysfunction. However, the molecular and cellular changes during the development of cardiac dysfunction are yet to be systematically studied. Similarly, the mechanism underlying autoimmune myocarditis is not very clear. However, a shared antigen between tumor cells and cardiomyocytes could become the target for activated T-cells, leading to myocardial lymphocytic infiltration showing clinical manifestation of heart failure (HF) and cardiac conduction abnormalities. [47]

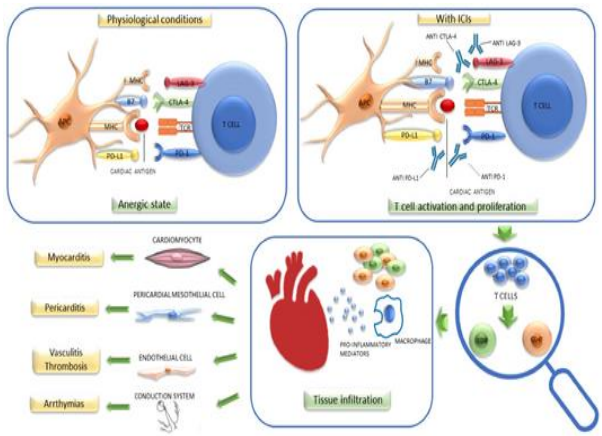

Fig.4: Pathogenetic mechanism of CD induced by ICIs

2. Methodology

The study does not attempt to test any specific a prior hypothesis, is largely descriptive, and utilises data collected only under conditions of routine clinical care. No additional invasive clinical tests or procedures are mandated per study protocol, and all data collected/extracted is based solely on observations of disease management and treatment decisions made between the treating physicians and their patients and is not intended to be interventional in anyway. Patients will not receive any experimental intervention or experimental treatment because of participating in this study.

Study design: This study is a retrospective and prospective observational single-centre study.

Ethics: The study data were gathered and informed consent was obtained in accordance with the Declaration of Helsinki. Study conduct was approved by the Institutional Ethics Committee. All patients were provided with written informed consent before participating.

Study period: The study was conducted for a period of 6 months

Study site: This study was conducted at Medicover Hospitals (Tertiary care hospital), Hi-Tech City, Hyderabad.

Sample size: Up to 55 Patients

Source of data:

The data was collected from the cancer patients after approval of the protocol by the IEC of Medicover. The patient would be followed up for a period of 6 months. Informed consent form would be prepared, and all participants would be provided written informed consent before enrolment.Subjects receiving Doxorubicin, Trastuzumab, Pembrolizumab, Nivolumab and meeting other inclusion criteria were enrolled in the study.

Study criteria

Inclusion Criteria:

- Patients should be Indians with age should be 18 years and above
- Patients diagnosed with cancer
- Patients who are receiving the following drugs for the first 6 months:
- Doxorubicin
- Trastuzumab
- Pembrolizumab
- Nivolumab

Exclusion Criteria:

- Patients who have recurrent cancer
- Patients who haven't given their consent

Criteria for evaluation

The following parameters will be monitored throughout the study. Follow up of the patients would be done 0-3-6 months to see the following parameters.

Demographic profile

- Age
- Sex
- BMI
- Comorbidities
- Family history of cardiac diseases
- Type of cancer

- Stage of cancer.

Parameters:

- EF
- GLS
- HS Troponin I

Statistical method:

EF (%), GLS (%), HS. Troponin I Were considered as primary outcome variables. Cardiotoxicity, population included and excluded, comorbidities were considered as Primary explanatory variable.For normally distributed Quantitative parameters the mean values were compared between study groups using independent sample t-test (2 groups). For non-normally distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups).Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test.P value < 0.05 was considered statistically significant. Data was analyzed by using SPSS software, V.22. (1)SPSS I. IBM SPSS Statistics Version 22 Statistical Software: Core System Users' Guide. SPSS Inc. 2014.

3. Results and Discussion

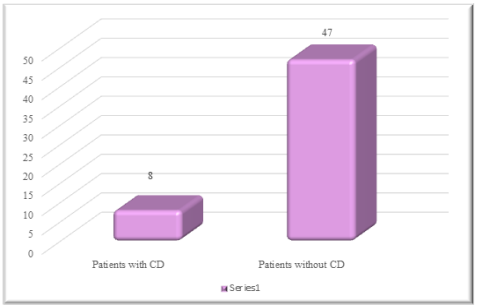

Fig.5: Percentage Incidence of CD by anti-cancer drugs

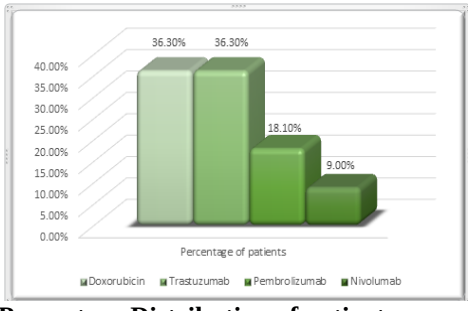

Fig.6: Percentage Distribution of patients according to the drug received

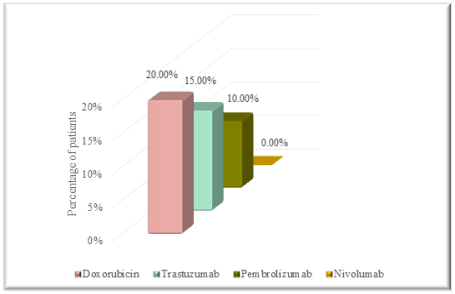

Fig.7: Percentage distribution of CD patients according to the drug received

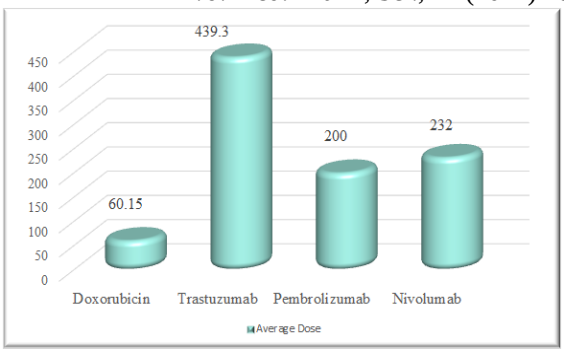

Fig.8: Distribution of drugs according to their average doses

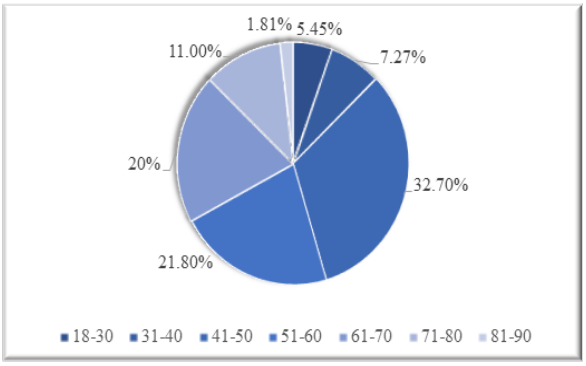

Fig.9: Percentage Distribution of patients according to age group

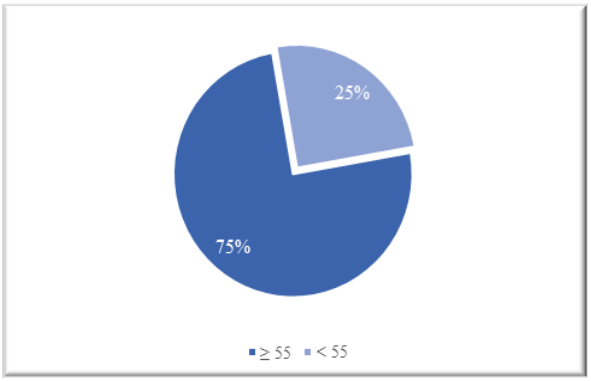

Fig.10: Percentage Distribution of CD patients according to age group

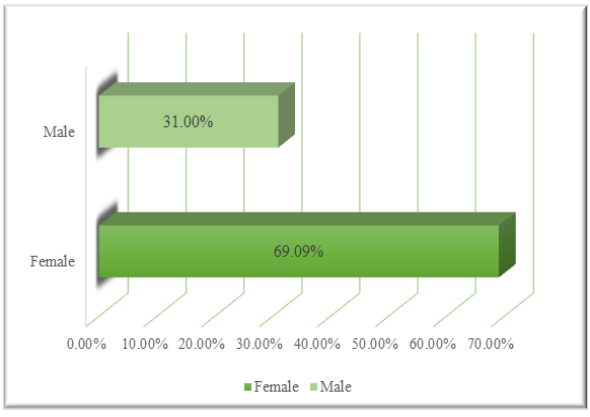

Fig. 11: Percentage distribution of patients according to sex

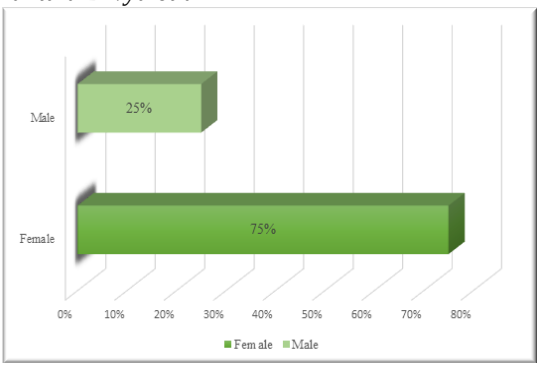

Fig.12: Percentage Distribution of CD patients according to sex

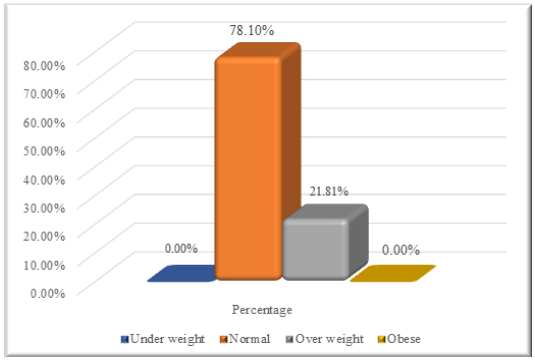

Fig.13: Percentage distribution of patients according to BMI

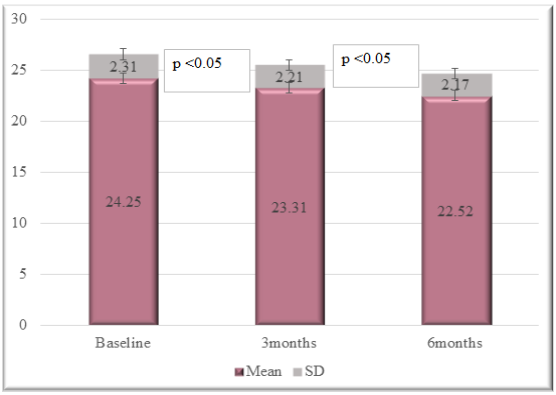

Fig.14: Describing the changes in BMI at different timelines

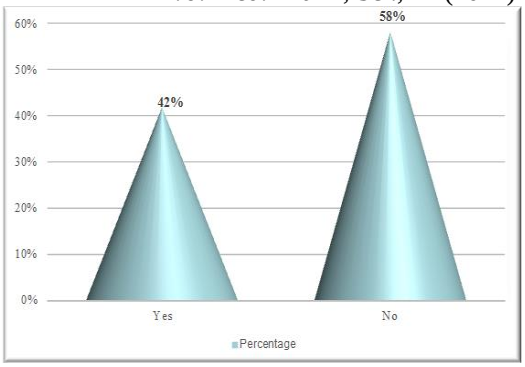

Fig.15: Percentage Distribution of patients according to family history of cardiac diseases

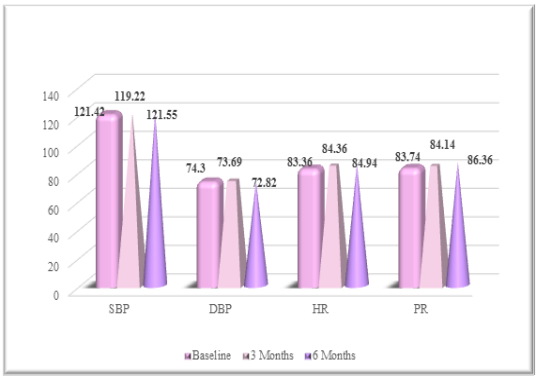

Fig.16: Describing the changes in vitals at different timelines

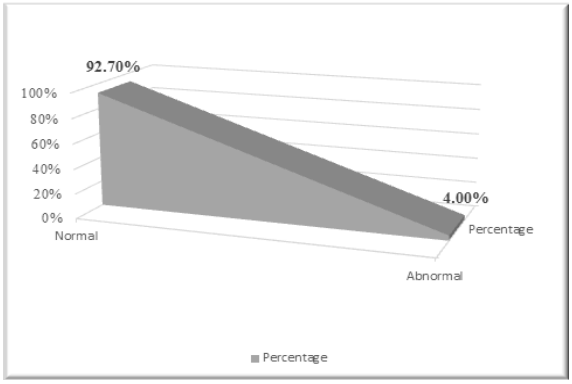

Fig.17: Percentage Distribution of patients according to HS Troponin-I

Table 1: Distribution of patients according to the drug received

S.NO	Drug Received	No. of patients	Percentage (%)
1.	Doxorubicin	20	36.30%
2.	Trastuzumab	20	36.30%
3.	Pembrolizumab	10	18.10%
4.	Nivolumab	5	9.00%

Table 2: Distribution of CD patients according to the drug received

S.NO	Drug Received	No. of patients with CD	Percentage (%)
1.	Doxorubicin	4	20 %
2.	Trastuzumab	3	15 %
3.	Pembrolizumab	1	10 %
4.	Nivolumab	0	0 %

Table 3: Distribution of drugs according to their average doses

S.NO	Drug	Average Dose (mg)
1.	Doxorubicin	60.15 mg
2.	Trastuzumab	439.3 mg
3.	Pembrolizumab	200 mg
4.	Nivolumab	232 mg

Table 4: Distribution of patients according to age group

S.NO	Age group of patients(years)	No. of patients	Percentage (%)
1.	18 – 30	3	5.45 %
2.	31 – 40 Y	4	7.27 %
3.	41 – 50 Y	18	32.7 %
4.	51 – 60 Y	12	21.8 %
5.	61 – 70 Y	11	20 %
6.	71 – 80 Y	6	11 %
7.	81 – 90 Y	1	1.81 %

Table 5: Distribution of CD patients according to age group

S.NO	Age (years)	No. of patients with CD	Percentage (%)
1.	≥ 55	6	75%
2.	< 55	2	25%

Table 6: Distribution of patients according to sex

S.NO	Sex	No. of patients	Percentage (%)
1.	Female	38	69.0
2.	Male	17	31.0

Table 7: Distribution of CD patients according to sex

S.NO	Sex	No. of patients with CD	Percentage (%)
1.	Female	6	75%
2.	Male	2	25%

Table 8: Distribution of patients according to BMI

S.NO	BMI	No. of patients	Percentage (%)
1	Under weight (<18.5)	0	0.00
2	Normal weight (18.5-24.9)	43	78.10
3	Overweight (25-29.9)	12	21.81
4	Obese (>30)	0	0.00

Table 9: Changes in BMI at different timelines

S.No	Parameter	Baseline	3 Months	P value	6 Months	P value
1.	BMI(Kg/m^2)	24.25±2.31	23.31±2.21	<0.05	22.52±2.17	<0.05

Table 10: Distribution of patients according to family history of cardiac diseases

S.NO	Family history of cardiac diseases	No. of patients	Percentage (%)
1.	YES	23	41.80 %
2.	NO	32	58.10 %

Table 11: Changes in Vitals at different timelines

S.NO	Parameter	Baseline	3 Months	P value	6 Months	P value
1.	SBP	121.42	119.22	0.233	121.55	0.942
2.	DBP	74.3	73.69	0.633	72.82	0.249

A retrospective and prospective observational study was conducted on incidence of cardiac dysfunction by anti-cancer drugs. It was a single centre study conducted in a tertiary care hospital for a period of 6 months where 55 individuals were enrolled.In present study we found an incidence of cardiac dysfunction by chemotherapy was 14.5%. This is similar with the reported studies in which the incidence was found to be 30% by the administration of doxorubicin and trastuzumab. [73] This reinforces the need for strict monitoring during the treatment.In our analysis, we found that 20% of patients with doxorubicin, 15% of patients with trastuzumab and 10% of patients with pembrolizumab had developed cardiac dysfunction. The highest incidence of cardiac dysfunction was found in doxorubicin followed by trastuzumab which is in accordance with the reported study (27%, 16%).[74]

In our study, the mean age of the patients diagnosed with cardiac dysfunction by anti-cancer drugs was found to be 58.25±8.2 that was not statistically significant (p=0.306). This is in accordance with the reported studies where the mean age was found to be 57.1±10.8 & 60±11 which was statistically significant (p=0.03) & (p=0.05).[75,76] Based on the above observation we found that advanced age is a factor that influences the risk of incidence of cardiac dysfunction by anti-cancer drugs. In present study, most of the patients were of the female population comprising nearly 69%. Cardiac dysfunction was mostly seen in the female population i.e., 6 (75%) with the administration of doxorubicin and trastuzumab. These findings are in compliance with the reported literature which shows that females (75%) are highly prone to develop cardiac dysfunction when compared to men.[62]

The present study findings are also contradicting with reported literature in which men (52%) are highly prone to develop cardiac dysfunction.[77] This might be due to enrolment of more female patients in our study.In our study, patients who have undergone treatment with doxorubicin & trastuzumab had a significant reduction in GLS from baseline to 3 months ($p < 0.05$ &<0.05) and 6 months ($p < 0.05$ &<0.05). Patients who have undergone treatment with Pembrolizumab & Nivolumab were seen with no significant difference from baseline to 3 months ($p > 0.05$ &>0.05) but in the 6th month, pembrolizumab showed a statistical significance ($p < 0.05$).

In our investigation, we found that there was a significant reduction in the GLS from 0-3 months and from 0-6 months about 2% & 4% respectively with a statistical significance of ($p< 0.05$). This is in accordance with the reported literature there is reduction in GLS from 0-3 months (2%,4.1%) and from 0-6 months (3%, 3.7%). [53,52]

To conclude, in anti-cancer drug induced cardiac dysfunction, GLS was found to be prognostically valuable. According to the present investigation, we found that a slight rise in HS Troponin-I is seen in cardiac dysfunction patients from baseline to 6 months. No studies have been reported about HS Troponin-I. This is the first study reporting it.

4. Conclusion

The patients administrated with chemotherapeutic drugs like Doxorubicin and Trastuzumab have a high probability to develop CD than patients who are administrated with immunotherapeutic drugs like Pembrolizumab and Nivolumab.Our study found a CD incidence of 14.5 % in patients who were given chemotherapeutic drugs.The incidence of CD was seen more in patients that have co-existing conditions such as diabetes and hypertension with females being more prone to it.GLS can be a critical parameter in monitoring early cardiac dysfunction in cancer patients.Further studies are needed to substantiate the outcomes of this study.

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