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RESEARCH ARTICLE

EVALUATION OF SYSTOLIC DYSFUNCTION IN PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS AFTER STEM CELL TRANSPLANT: A SINGLE CENTER EGYPTIAN EXPERIENCE.

Haitham Mohammed Abdelbary, Yasmin Ahmed Abou El Magd, Gihan Kamal Shams Eldin and Mohamed Osman Azzazi.

Clinical Hematology and Bone Marrow Transplantation Unit, Division of Internal Medicine, Ain Shams University, Cairo, Egypt.

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Abstract

Background: The long-term prognosis after Hematopoietic stem cell transplantation (HSCT) has greatly improved. However, HSCT survivors are at risk of developing long term complications. Cardiac complications are potentially life-threatening and there is a need to elucidate the incidence, severity and underlying mechanisms of these complications. We assessed the systolic cardiac function by echocardiography in patients who underwent autologous and allogeneic hematopoietic stem cell transplantation for lymphoproliferative disorders and evaluated the association between the conditioning regimens used and the decline in ejection fraction.

Materials and methods: 100 patients were enrolled in this retrospective study, 72 patients underwent autologous and 21 patients underwent allogeneic stem cell transplantation. 39 patients had multiple myeloma, 30 patients had NHL, 21 patients had acute lymphoblastic lymphoma, 10 patients had HD. LVEF was assessed by echocardiography and compared to a healthy control group as well as 50 positive control of patients who received chemotherapy without undergoing transplant.

Results: The mean ejection fraction of cases after transplant is significantly reduced compared to the negative control group, The ejection fraction decline was highly pronounced in older age groups, male patients and more in patients with larger surface area, with the use of TBI-based regimens followed by patients who received high-dose cyclophosphamide in the conditioning regimens.

Conclusion: LVEF was reduced in patients with lymphoproliferative disorders after autologous and allogeneic hematopoietic stem cell transplantation and was correlated with the use of TBI-based conditioning regimens and high-dose cyclophosphamide.

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Introduction:-

Allogeneic or autologous HSCT offers a possibility of cure or long-term remission in hematological malignancies. However, gastrointestinal, pulmonary, infectious and immunological complications are major problems and limiting factors for HSCT¹.

Corresponding Author:- Haitham Mohammed Abdelbary.

Address:- Clinical Hematology and Bone Marrow Transplantation Unit, Division of Internal Medicine, Ain Shams University, Cairo, Egypt.

Finally, in the last few years reduced-intensity conditioning regimens have been applied to patients undergoing allogeneic HSCT to reduce drug toxicity while maintaining the potential for achieving disease remission exploiting the graft-versus-leukemia effect².

The long-term prognosis after haematopoietic stem cell transplantation (HSCT) has greatly improved. However, HSCT survivors are at risk of developing long term complications, and mortality rates remain four- to ninefold higher than in the general population³.

Cardiac complications have been documented in several series, with reported incidence varying among investigators from 0 to 43%, and mortality up to 9% in earlier studies¹.

Cardiovascular complications can be grouped into three main categories: vascular abnormalities, cardiac structural problems and myocardial dysfunction and heart failure.

Evaluation of cardiac toxicity in patients includes consideration of biomarkers such as cardiac troponins and B-type natriuretic peptides, together with noninvasive imaging in the form of 2D-, 3D-, or strain echocardiography, multiple gated radionuclide angiography, quantitative gated blood-pool SPECT, or cardiac magnetic resonance imaging³.

The purpose of this study is to evaluate systolic dysfunction in patients with lymphoproliferative disorders after hematopoietic stem cell transplantation.

Patients and Methods:-

Study Design:-

Patients and Control:-

The study was conducted in the bone marrow transplantation unit (department of clinical hematology at Ain Shams university hospital) during a period from June 2015 to August 2016.

Participants were grouped into:-

Group (1): included 100 patients with lymphoproliferative disorders who underwent BMT in our unit, 79 patients underwent autologous transplant and 21 underwent allogeneic transplant, 30 patients with NHL, 10 patients with HD, 39 patients with multiple myeloma and 21 patients with acute lymphoblastic leukemia.

Group (2) (healthy control group): included participants without known cardiovascular disease, hypertension or DM. They were matched 1:1 based on age, sex, blood pressure and surface area with the cases.

Group (3) (positive control): 50 patients with lymphoproliferative disorders who received chemotherapy without undergoing BMT. They included 25 males and 25 females, 46% had MM, 42% had NHL and 12% had HD.

Informed consents were obtained from all participants. The study was conducted in accordance with the stipulations of the local ethical and scientific committees of Ain Shams University and the procedures respected the ethical standards in Helsinki declaration of 1964.

Methods:-

All patients were subjected to full history and physical examination including the presence of B-symptoms like weight loss, fever, drenching sweats and pruritis, anemic manifestations or bleeding or the presence of bone fractures and the presence of lymphadenopathies or hepatosplenomegaly.

To confirm the diagnosis of NHL and HD:-

- Excision lymph node biopsy for fresh frozen and formaline-fixed samples for histopathological assessment.
- Immunohistochemistry for B-cell markers like CD20,CD19,CD79a,CD10 and T-cell markers like CD3,CD4,CD8,CD7,CD5,CD2 , markers of immature lymphoblast like TdT, immunoglobulin Kappa and Lambda light chain restriction and for CD15 and CD30 for characterization of Reed-Sternberg cells.
- Chest X-ray, contrast-enhanced CT scans of the neck, chest and pelviabdomen.
- Baseline, interim and end of therapy PET was carried out whenever available for staging and response assessment.

- Bone marrow aspiration and trephine biopsy.
- Cytogenetic analysis using conventional cytogenetics and FISH for certain specific chromosomal abnormalities.
- Staging is carried out according to Ann-Arbor staging system Examination.
- Cerebrospinal fluid and triple intrathecal chemotherapy prophylaxis was given to certain patients like: (1): patients with DLBCL with bone marrow, testicular, paranasal and epidural involvement. (2): lymphoblastic lymphoma. (3): primary CNS lymphoma.
- Upper GI endoscopy in those with suspected GI involvement eg. Mantle cell lymphoma.

To confirm the diagnosis of multiple myeloma:-

- Complete blood counts and serum chemistries especially for serum calcium, serum creatinine to detect CRAB features.
- Detection of monoclonal M-protein in the serum and urine by serum protein electrophoresis.
- Characterization of heavy and light chains in the serum and urine sample by immunofixation.
- Bone marrow aspiration and biopsy to evaluate the percentage of plasma cells.
- Conventional chromosomal analysis and FISH for high-risk myeloma like t(4;14), (14;16) and 17p.
- Skeletal survey for evaluation of lytic bone lesions using X-ray of spine, skull, pelvis, humerus and femur.
- MRI to evaluate symptomatic bony sites even if skeletal survey is negative or in case of spinal cord compression.
- Serum free light chains and Kappa/Lambda ratio for the detection of stringent CR whenever possible.

To confirm the diagnosis of acute lymphoblastic leukemia:-

- Complete blood count and differential for the detection of peripheral blasts.
- Bone marrow aspiration and trephine biopsy for the detection of the percentage of blast cells.
- Immunophenotyping for lymphoid and myeloid markers.
- Conventional cytogenetics and FISH for Philadelphia chromosome.
- CT scans for the neck, chest and pelviabdomen.
- CSF examination and triple intrathecal chemotherapy for prophylaxis and/or therapy in case of CNS involvement.

Patients who underwent autologous transplant were subjected to:-

- Complete blood count using (LH Beckman coulter).
- Serum chemistries including liver and renal function tests (AU 680 chemistry autoanalyzer).
- Viral markers for hepatitis B, hepatitis C and HIV using Rosh diagnostics and performed by copus instruments.
- Polymerase chain reaction (PCR) for CMV using kits supplied by Qiagen and performed by rotor gene instrument for automated real time PCR.
- Serology for herpes simplex (HSV), Toxoplasma and Epstein Bar virus (EBV).
- Pulmonary function tests.
- Renal scan.
- Electrocardiogram and echocardiography.
- Mobilization was done using different regimens ranging from G-CSF alone to G-CSF and cyclophosphamide or other chemotherapeutic regimen depending on the specific disease.
- Conditioning regimens: for patients with MM high dose melphalan 200mg/m² on day -2, for patients with NHL and HD they received a conditioning regimens consisted of cyclophosphamide 60mg/kg/d -3 and -2, etoposide 15mg/kg/d -3 and -2, carboplatin 400mg/m² -3 and -2.

In addition, patients undergoing allogeneic transplant are subjected to:-

- Donors received (after informed consent) 4 days of treatment with SC G-CSF (10ug/kg/d) before stem cells were collected.
- Mononuclear cells were isolated using a Cobe Spectra separator (Lakewood, Co, USA).
- The number of CD34 cells transfused was calculated using flowcytometric analysis.
- GVHD prophylaxis consisted of cyclosporine and methotrexate.
- Engraftment was defined as absolute neutrophilic count of more than 500 for three consecutive days.
- Chimerism analysis by variable number of tandem repeats (VNTR) was done at +28 and +56 after transplant.

- Conditioning regimen consisted of TBI 2.5GY days -7 to -4 /Cyclophosphamide 60mg/kg days -3 and -2, TBI 2.5 GY days -7 to -4 /etoposide 60mg/kg d-3, Fludarabine 30mg/m² days -6 to -2 /oral Busulfan 1mg/kg/6hours days -6 to -3.

All patients in both autologous and allogeneic transplant were treated using the same anti-infectious and transfusion policy of our transplant center.

Transthoracic echocardiography:-

- All patients were evaluated during transplant in case of occurrence of any minor or major cardiac events according to the international guidelines recommended by ACC and AHA.
- Transthoracic echocardiography was done before transplant and 6 months after transplant.
- Transthoracic echocardiography was carried out using 2-4 MHz phased array transducer attached to a vivid S5 echocardiography machine by a cardiologist who was blinded to clinical details of each subject. Inter-observer variability was reduced by taking the mean of three reading during each echocardiography.
- The following parameters were examined: left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD), intraventricular end-diastolic diameter (IVSDD), posterior wall end-diastolic diameter (PWEDD), right ventricular end-diastolic diameter (RVEDD), left atrium diameter (LA) and aorta diameter (Ao). The systolic function was determined by left ventricular ejection fraction (LVEF) using M-mode and modified Simpson's formula. Left ventricular diastolic function was evaluated with pulsed Doppler and tissue Doppler imaging (TDI). The following parameters of the diastolic function of left ventricle were determined: early filling velocity E wave (E) and A wave (A) of mitral inflow, Doppler-derived mitral deceleration time of early filling (DT), isovolumetric relaxation time (IVRT) and early diastolic velocity of mitral annulus wave (E0).

Statistical analysis:-

- All analyses of the present study were done using SPSS version 17 software.
- Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation, student t-test, chi square.
- Data were expressed as mean value \pm SD for continuous variables, and as percentages for categorical variables. In this study, statistical significance was established as follows: $p > 0.05$ insignificant, $p \leq 0.05$ significant, $p \leq 0.01$ highly significant.
- Comparisons between continuous variables were performed using the paired t-test or unpaired t-test. For comparisons of categorical variables, frequency tables and chi-square tests were used.

Results:-

100 patients were enrolled into the study (39 patients with MM, 30 patients with NHL, 10 patients with HD and 21 patients with ALL) (table 1). There were 50 males and 50 females, 55 patients aged <45 years, 21 aged 45-55 years and 24 aged >55 years (table 5). Healthy control group included participants without known cardiovascular disease, hypertension or DM. They were matched 1:1 based on age, sex, blood pressure and surface area with the cases. Positive control included 50 patients with lymphoproliferative disorders who received chemotherapy without undergoing BMT. They included 25 males and 25 females, 46% had MM, 42% had NHL and 12% had HD. 72 patients underwent autologous and 21 patient underwent allogeneic stem cell transplantation (figure 1).

Table 1:- Percentages of patients with lymphoproliferative disorders in our study:

Lymphoproliferative disorder		
	N	%
MM	39	39.00
NHL	30	30.00
HD	10	10.00
ALL	21	21.00
Total	100	100.00

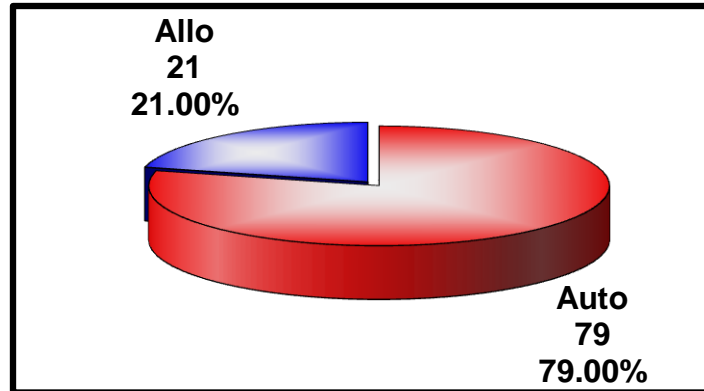


Figure 1:- Percentages of autologous and allogeneic stem cell transplant patients in our study group.

The mean ejection fraction of cases after transplant is significantly reduced compared to the negative control group with highly statistically significant difference (P-value <0.001) (table 2). There is a highly statistically significant difference between ejection fraction in the initial echocardiography before therapy in all patients and the follow up echocardiography after either chemotherapy only in group III or transplanted patients in group I (P-value<0.001).

Also, these results show that group I (transplant group) had higher initial ejection fractions compared to group III with highly statistically significant difference by using unpaired t-test (P-value <0.001) (table 3).

Table 2:- The mean ejection fraction of group I patients that underwent transplant and that of healthy group II (negative control) included in the study:

ECHO	GROUPS		T-test	
	Group I (cases) after transplant	Group II (Negative control)	T	P-value
Range	49-70	59-75	-5.322	<0.001*
Mean \pm SD	59.590 \pm 6.299	66.760 \pm 4.728		

Table 3:- Correlation between the ejection fraction in the initial echocardiography before therapy in all patients and its decline in the follow up echo after either chemotherapy only in group (3) or transplant in group (1):

Echo		Group I (cases)	Group III (Positive control)	T-test	
				T	P-value
Initial echo	Range	55-75	52-73	5.261	<0.001*
	Mean \pm SD	67.290 \pm 4.123	62.880 \pm 6.033		
Follow up echo	Range	49-70	45-62	5.883	<0.001*
	Mean \pm SD	59.590 \pm 6.299	53.820 \pm 4.084		
Paired difference	Mean \pm SD	7.700 \pm 5.519	9.060 \pm 5.464		
Paired samples test	T	13.953	11.725		
	P-value	<0.001*	<0.001*		

Conditioning regimens used during transplant included high dose melphalan in 39 patients with multiple myeloma, Cyclophosphamide/Carboplatin/Etoposide in 36 patients with NHL and HD, Fludarabine/Busulfan and TBI-based regimens in patients with ALL (table 4).

Table 4:- Percentages of conditioning regimens used in our study:

Conditioning regimen		
	N	%
High dose melphalan	39	39.00
Cyclophosphamide/Carboplatin/Etoposide	36	36.00
Fludarabine/Busulfan	14	14.00
TBI-based	11	11.00
Total	100	100.00

Chemotherapy regimens used prior to transplant included hyperCVAD/Holezer protocols for patients with ALL, VAD/CVAMP for MM, ABVD/GDP for HD and CHOP/DHAP for NHL (figure 2).

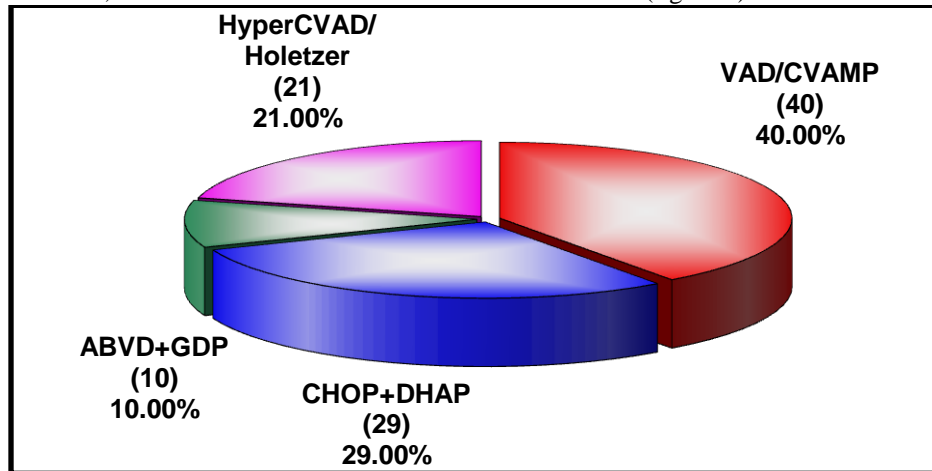


Figure 2:- Type of chemotherapy used prior to transplant

The ejection fraction decline was highly pronounced in older age groups compared to younger group with highly statistically significant difference (P-value 0.001) (table 5). The ejection fraction decline was seen more in male cases compared to females (P-value 0.009) (table 5). Also, the decline of ejection fraction was more in patients with surface area >1.8 than those with surface area <1.8 (P-value 0.040) (table 5). There is no statistically significant difference between the type of transplant and the decline in ejection fraction (table 5).

Table 5:- Relation of the different age groups, sex, surface area and type of transplant of the cases and the decline in their ejection fraction:

	EF decline						Chi-Square	
	Negative		Positive		Total		X ²	P-value
	N	%	N	%	N	%		
Age Groups							13.638	0.001*
<45 Years	52	63.41	3	16.67	55	55.00		
45-55 Years	15	18.29	6	33.33	21	21.00		
>55 Years	15	18.29	9	50.00	24	24.00		
Total	82	100.00	18	100.00	100	100.00		
Sex							6.775	0.009*
Male	36	43.90	14	77.78	50	50.00		
Female	46	56.10	4	22.22	50	50.00		
Total	82	100.00	18	100.00	100	100.00		
Surface area >1.8							4.225	0.040*
Negative	40	48.78	4	22.22	44	44.00		
Positive	42	51.22	14	77.78	56	56.00		
Total	82	100.00	18	100.00	100	100.00		
Type of transplant							2.013	0.156
Auto	67	81.71	12	66.67	79	79.00		
Allo	15	18.29	6	33.33	21	21.00		
Total	82	100.00	18	100.00	100	100.00		

There is a statistical significance between the decline in ejection fraction and the conditioning regimen used for the transplant with patients in the TBI-based regimens are more affected followed by patients who received high dose cyclophosphamide (table 6).

Comparing TBI-based regimens to non-TBI regimens there is highly statistically significant difference between the decline in ejection fraction and the use of TBI (P-value 0.012) (table 7).

Table 6:- Correlation between the conditioning regimens used to prepare group (1) patients and the decline in ejection fractions:

Conditioning regimen	EF decline						Chi-Square	
	Negative		Positive		Total		X ²	P-value
	N	%	N	%	N	%		
Melphalan	36	43.90	3	16.67	39	39.00	8.587	0.035*
Endoxan/Carboplatin/Etoposide	29	35.37	7	38.89	36	36.00		
Fludarabine/Busulfan	11	13.41	3	16.67	14	14.00		
TBI-based	6	7.32	5	27.78	11	11.00		
Total	82	100.00	18	100.00	100	100.00		

Table 7:- Correlation between the use of TBI-based conditioning regimens to prepare cases and decline in their ejection fraction:

Conditioning regimen TBI	EF decline						Chi-Square	
	Negative		Positive		Total		X ²	P-value
	N	%	N	%	N	%		
Negative	76	92.68	13	72.22	89	89.00	6.312	0.012*
Positive	6	7.32	5	27.78	11	11.00		
Total	82	100.00	18	100.00	100	100.00		

Discussion:-

The current standard for cardiac monitoring during cancer therapy is mainly based on LVEF assessment, but it can underestimate early potentially progressive cardiotoxicity, and preserved cardiac function is generally required for enrollment in clinical trials of high dose chemotherapy. This is commonly defined as LVEF>50% and no other significant cardiac disease.

Many studies reported a significant association between pretransplant LVEF and cardiotoxicity. However, measurement of LVEF before high dose chemotherapy is not the only determinant factor as 2/3 major cardiac events reported in patients with normal LVEF².

In the current study, we found that the mean ejection fraction of cases after transplant is significantly reduced compared to the negative control group with highly statistically significant difference (P-value <0.001). Also, there is a highly statistically significant difference between ejection fraction in the initial echocardiography before therapy in all patients and the follow up echocardiography after either chemotherapy only in group III or transplanted patients in group I (P-value<0.001).

A wide variety of conditioning regimens have been used prior to stem cell transplantation. Including, TBI-based regimens and high-dose cyclophosphamide, and cardiac toxicity has been associated mostly with the use of these regimens with a wide spectrum of incidence, manifestation and severity.

HD cyclophosphamide-associated cardiac toxicity is thought to depend upon toxic endothelial damage followed by extravasation of toxic metabolites with resultant myocyte damage and interstitial hemorrhage and edema. HD cyclophosphamide-associated cardiotoxicity occurs during or soon after (within 3 weeks) administration. It is manifested clinically as acute or subacute onset of congestive heart failure (CHF) with pulmonary congestion, weight gain and oliguria. Pericardial effusion, in some cases with cardiac tamponade. Although HD cyclophosphamide-associated cardiac toxicity is potentially reversible, in patients who develop severe, progressive CHF, this complication may lead to death within few weeks².

In our study, we found that ejection fraction decline is higher in patients with a body surface area >1.8 than those with a body surface area <1.8 reflecting a higher dosage of chemotherapeutic agents used in those patients.

In fact, optimal chemotherapy dosing in obese patients is one of the most controversial aspects of HD chemotherapy since obese patients have altered pharmacokinetics for many medications including chemotherapeutic agents when compared with the non-obese.

Indeed, association of obesity with cardiac toxicity can be spotted throughout the literature. As a practical approach, reduction of HD cyclophosphamide dosage in patients whose actual BW exceeds by >20% of the IBW is a safety measure that doesn't affect the efficacy of chemotherapy and minimizes the risk of toxicity².

In the current study, the ejection fraction decline was highly pronounced in older age groups compared to younger group with highly statistically significant difference (P-value 0.001). The ejection fraction decline was seen more in male cases compared to females (P-value 0.009).

The comparison between autologous and allogeneic recipients is especially important. More pronounced cardiotoxic effects could be expected in allogeneic recipients as a result of a different spectrum of conditioning regimens, infectious complications and also an effect of GVHD.

In our study, no difference was found between the incidence of EF decline and the type of transplant. However, the number of allo HSCT in this study is much fewer than the auto patients.

Hernstein et al found that despite the speculation of higher incidence of cardiotoxic complications in patients undergoing allo-HSCT, a higher incidence heart failure was found in autologous recipients in their study. However, the number of autologous patients in their study was small⁴.

There is a statistical significance between the decline in ejection fraction and the conditioning regimen used for the transplant with patients in the TBI-based regimens are more affected followed by patients who received high dose cyclophosphamide.

Comparing TBI-based regimens to non-TBI regimens there is highly statistically significant difference between the decline in ejection fraction and the use of TBI (P-value 0.012).

The epidemiology of RICVD is complicated by the continual improvements in radiation dosimetry and shielding that tend to reduce cardiovascular exposure and the latent effects of radiation, which takes years or decades to manifest.

Several large studies have been published over the last few years that analyzed the outcome of RT administered between one and four decades ago.

Radiation-induced pericarditis is the earliest form of RICVD to occur following mediastinal irradiation. It may occur in either of two forms, early and acute or delayed and chronic, which should be regarded from a histopathological standpoint as two distinct disease entities⁵.

The risk of radiation-induced cardiomyopathy increases after 5 years, but it can evolve decades after initial RT⁶. Pathologically, RICM is characterized by inflammation followed by the development of a diffuse, patchy interstitial fibrosis of the myocardium and effacement of perimyocyte and endothelium⁷.

More recently, researchers at the Netherlands Cancer Institute found a stepwise decrease in 30-year cumulative incidence of valvular heart disease (VHD) corresponding to diminishing doses of RT, from 12.4% at doses greater than 40 Gy to 3.0% at doses less than 30 Gy⁸.

A large case control study of breast cancer survivors in Denmark and Sweden undertaken in 2013 found that the risk of a major CHD event begins to increase within the first 5 years post-treatment and continues to significantly exceed that of the general population through at least 20 years of follow-up. These patients experienced increased risk of angina pectoris, MI, and sudden cardiac death despite having been treated with a modest mean heart dose of 3.6 Gy RT between 1958 and 2001⁹.

Another large study of women in Denmark and Sweden ($n = 35000$) comparing incidences of MI in breast cancer survivors observed an incidence ratio of 1.22 in patients undergoing left-sided vs right-sided RT¹⁰.

In the current study 36.4% of lymphoma patients that underwent autologous transplant with cyclophosphamide-based regimens developed a decline in their LVEF. Previous reports showed that CY cardiotoxicity is correlated with the dose of CY is being higher in patients received 200 >120 >100 mg/kg¹¹.

In a previous report, higher age, administration of cyclophosphamide and higher glucose concentrations represented independent risk factors for the worsening of left ventricular diastolic function¹².

Several methods were investigated to reduce anthracycline cardiotoxicity, most cardioprotective strategies are not in common clinical practice. Other approaches to mitigate the cardiotoxic impact of anthracyclines employ potentially cardioprotective medications, such as ACE inhibitors and beta blockers. Although promising data have been published recently, convincing evidence from large randomized and prospective trials is still needed³

There are some limitations of our current analysis. First, this was a retrospective study from a single institution. Second, early CY-induced cardiotoxicity appears to be characterized by LV diastolic rather than systolic dysfunction.

Conclusion:-

LVEF was reduced in patients with lymphoproliferative disorders after autologous and allogeneic hematopoietic stem cell transplantation and was correlated with the use of TBI-based conditioning regimens and high-dose cyclophosphamide.

References:-

1. **Lehmann S, Isberg B, Ljungman P, et al.** Cardiac systolic function before and after hematopoietic stem cell transplantation. *Bone marrow transplantation* 2000; 26(2): 187-192.
2. **Morandi P, Ruffini PA, Benvenuto GM.** Cardiac toxicity of high-dose chemotherapy. *Bone marrow transplantation* 2005; 35(4): 323-324.
3. **Roziakova L, Mistrik M, Batorova A.** Can We Predict Clinical Cardiotoxicity with Cardiac Biomarkers in Patients After Haematopoietic Stem Cell Transplantation? *Cardiovasc Toxicol* 2015; 15:210–216.
4. **Hertenstein B, Stefanic M, Schmeiser T et al.** Cardiac toxicity of bone marrow transplantation: predictive value of cardiologic evaluation before transplant. *J Clin Oncol* 1994; 12:998–1004.
5. **Cuomo JR, Sharma GK, Conger PD et al.** Novel concepts in radiation-induced cardiovascular disease. *World journal of cardiology* 2016; 26; 8(9): 504-519.
6. **Aleman BM, van den Belt-Dusebout AW, De Bruin ML et al.** Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;109: 1878-1886.
7. **Heidenreich PA, Kapoor JR.** Radiation induced heart disease: systemic disorders in heart disease. *Heart* 2009; 95: 252-258.
8. **Cutter DJ, Schaapveld M, Darby SC et al.** Risk of valvular heart disease after treatment for Hodgkin lymphoma. *J Natl Cancer Inst* 2015; 107(4):djv008.
9. **Darby SC, Ewertz M, McGale P et al.** Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987-998.
10. **McGale P, Darby SC, Hall P et al.** Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden. *Radiother Oncol* 2011; 100: 167-175.
11. **Ishida S, Doki N, Shingai N et al.** The clinical features of fatal cyclophosphamide-induced cardiotoxicity in a conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT). *Ann Hematol* 2016; 95:1145-1150.
12. **Poręba M, Gać P, Usnarska-Zubkiewicz L.** Echocardiographic evaluation of the early cardiotoxic effect of hematopoietic stem cell transplantation in patients with hematologic malignancies. *Leukemia and lymphoma* 2016; 57(9): 2119-2125.