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Echocardiographic Assessment of Right Ventricular Function and Pulmonary Arterial Pressure in Patients with Multiple Myeloma Post Autologous Hematopoietic Stem Cell Transplantation

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ABSTRACT

Background: Multiple myeloma [MM] is the second most common type of cancer affecting the blood and bone marrow. Autologous hematopoietic stem cell transplantation [auto-HSCT] has helped improve survival rates for multiple myeloma patients. However, the standard preparative regimen with melphalan can have cardiotoxic effects.

The aim of the work: We aimed to investigate the potential utility of echocardiography in evaluating right ventricular [RV] function and estimating systolic pulmonary arterial pressure [sPAP] for the early detection of cardiotoxicity in multiple myeloma patients following auto-HSCT. The primary aim was to reduce cardiac morbidity and mortality and facilitate future preventive measures.

Patients and Methods: This prospective study included data from 30 multiple myeloma patients planned to undergo auto-HSCT at the Cardiovascular Department of Sheikh Zayed Specialized Hospital in Giza, Egypt. Patients underwent echocardiographic assessment, including measurements of TAPSE, tricuspid annular S' velocity, FAC, and RIMP one day before and 30 days after conditioning with high dose melphalan.

Results: Comparing pre- and post-auto-HSCT echocardiogram data, there were statistically significant drops in TAPSE, tricuspid annular S' velocity, FAC and a rise in RIMP post-transplant [P <0.001, P < 0.001, P = 0.009, P < 0.001 respectively].

Conclusion: Early RV systolic dysfunction occurs post-auto-HSCT in multiple myeloma patients conditioned with high-dose melphalan.

Keywords: Multiple myeloma; Autologous Hematopoietic Stem Cell Transplantation; Melphalan; Cardiotoxicity; Right ventricle.

INTRODUCTION

Patients with high-risk hematological malignancies, such as Multiple Myeloma, may benefit from hematopoietic stem cell transplantation [HSCT], which is sometimes the only curative therapeutic option [1]. Acute cardiotoxicity includes a spectrum of cardiac complications that may arise within the initial 100 days following HSCT. These complications include heart failure, pulmonary edema, pulmonary hypertension, pericarditis, arrhythmia, and sudden cardiac death. Numerous investigations have demonstrated that individuals who undergo transplantation procedures are susceptible to experiencing post-transplant acute cardiac complications, which have been associated with a mortality rate of 1.2%. Furthermore, the incidence of morbidity resulting from these complications has been observed to vary within a range spanning from 5% to 43% [2].

The standard preparative regimen for patients with Multiple Myeloma who are undergoing auto-HSC involves the administration of high-dose melphalan at a dosage of 200 mg/m^2, commonly referred to as Mel200 [3].

Melphalan, an alkylating agent, elicits cardiotoxic effects through the induction of oxidative stress, impairments in calcium ion [Ca^{2+}] handling, compromised contractility, perturbations in global transcriptomic and proteomic profiles, ultimately leading to apoptosis and cellular demise [4]. The incidence of newly-developed heart failure was documented to range from 4.8% at 5 years and 9.1% at 15 years following auto-HSCT [5].

Left sided Heart failure [LSHF] is the most serious of cardiac complications [6]. To date, the existing medical armamentarium lacks a treatment modality capable of inducing scar tissue regeneration within the standard therapeutic approach for heart failure [HF], thereby contributing to escalated rates of both mortality and morbidity [7].

Early detection of heart failure [HF] is highly recommended by the European Society for Medical Oncology [ESMO] and necessitating echocardiographic follow up for left ventricular function for recipients of HSCT [8].

Previous researches conducted on recipients of HSCT has predominantly concentrated on the structure and function of the left ventricle so our study, in particular, aimed to assess right ventricular function, an aspect often missed during examinations.

Pulmonary hypertension [PH] has been identified as a potentially life-threatening complication associated with auto-HSCT [9]. Consequently, early detection of PH has emerged as an important aspect in our study.

PH is a medical condition characterized by the presence of mean pulmonary artery pressure [mPAP] exceeding 20 mmHg during periods of rest. Right heart catheterization, an established diagnostic modality, is widely regarded as the gold standard in the field. However, it is worth noting that this particular method may not be deemed suitable for routine, everyday clinical application [10].

In the past three decades, remarkable advancements in the field of echocardiography have enhanced its capacity to detect and measure pulmonary artery pressure [PAP]. Consequently, this non-invasive imaging technique has emerged as a viable and secure substitute for invasive catheterization, offering a readily accessible means of assessing PAP levels [11].

The aim of the present study is to investigate whether assessment of right ventricular [RV] function and estimation of [sPAP] systolic pulmonary arterial pressure by echocardiography may help in early diagnosis of cardiotoxicity for patients with Multiple Myeloma post auto-HSCT and thus decrease cardiac morbidity and mortality and help for future prevention.

PATIENTS AND METHODS

Our study was performed prospectively on thirty patients diagnosed with Multiple Myeloma. All patients were candidate for auto-HSCT. Assessment was performed a day before and thirty days after conditioning with high dose Melphalan and auto-HSCT [melphalan 200 mg/m^2 before HSCT]. The study was performed at cardiovascular department, Sheikh Zayed Specialized Hospital, Giza, Egypt, from January 2023 to July 2023.

Our study was approved from the ethical committee of the same institution. Helsinki declaration principals were followed in this study. We recruited the patients according to the following criteria:

The Inclusion criteria: Multiple Myeloma patients who were planned to undergo auto-HSCT and their age ranged from 18 to 70 years.

The Exclusion criteria: Patients with history of Anthracycline therapy, patients with poor echogenicity, patients known to have ischemic heart disease, patients with arrhythmia or conduction abnormalities and patients with significant valvular heart disease.

Data collection: It included the followings: History taking, Clinical examination, Laboratory investigations including serum Hemoglobin , electrolytes and Troponin, Standard 12-leads ECG and conventional echocardiographic assessment of LV diameters and LV ejection fraction using M-Mode, LV diastolic function using pulse wave doppler, RV linear diameters, systolic PAP, PAT and RV systolic function using TAPSE, tricuspid annular S', fractional area change [FAC] and RV index of myocardial performance [RIMP] using tissue doppler imaging [TDI]. Transthoracic echocardiography was performed upon admission utilizing the X 5-1 MATRIX ARRAY probe, which operates within a frequency range of 1.5-4.3 MHz. This probe was connected to the SIEMENS ACUSON NX3 ultrasound machine. The patients underwent examination while in the left lateral position at the conclusion of expiration, under the supervision of the same echocardiologist, adhering to the guidelines set forth by the European Association of Cardio-vascular Imaging [EACVI].

Statistical analysis: The collection, revision, coding, and entry of data were performed, followed by their incorporation into the Statistical Package for Social Science [IBM SPSS] version 20. The presentation of the data involved the utilization of both qualitative and quantitative measures. Qualitative data were expressed in numerical form, specifically as numbers and percentages. On the other hand, quantitative data with a parametric distribution were represented using the mean and standard deviations. A comparative analysis was conducted to assess the quantitative data with parametric distribution before and after treatment. This analysis employed the paired t-test method to evaluate the differences between the two time points.

RESULTS

Regarding the demographic characteristics of the cohort under investigation, the age range spanned from 35 to 63 years, with a calculated mean value of 47.53±7.537 years. The study population consisted of 30 individuals, with 19 [63.3%] being male and 11 [36.7%] being female [Table 1].

Concerning patients' risk factors; 10[33.3%] had DM, 6[20.0%] had HTN, 6[20.0%] had dyslipidemia, 2[6.7%] had family history and 4[6.7%] were smokers [Table 2].

There was no statistically significant difference in serum levels of Hemoglobin, Sodium, Potassium and Troponin I levels before and after procedure. [12.33 ± 0.852 vs. 11.97 ± 0.904, P=0.256; 138.47 ± 2.488 vs. 135.83 ± 3.130, P < 0.001; 3.95 ± 0.261 vs. 3.59 ± 0.296, P = 0.225; 0.02 ± 0.014 vs. 0.04 ± 0.086, P=0.109, respectively] [Table 3].

The differences in echocardiographic para-meters including left ventricular end-diastolic diameter, left ventricular end-systolic diameter, left ventricular ejection fraction, E/A ratio, RV linear dimensions, systolic pulmonary artery pressure [sPAP] and Pulmonary acceleration time [PAT] before and after auto-HSCT was not significant statistically.

Importantly, there were highly statically significant difference between pre-transplant values and post-transplant values of the tricuspid annular plane systolic excursion [TAPSE], tricuspid annular S' velocity, tissue doppler right ventricular index of myocardial performance [RIMP] and fractional area change [FAC] [2.21 ± 0.12 vs. 1.61 ± 0.20, P = < 0.001; 0.38 ± 0.02 vs. 0.54 ± 0.07, P < 0.001, 48.93 ± 2.463 vs. 35.73 ± 2.947, P = 0.009; respectively] [Table 4].

Table [1]: Demographics data of the patients

	Number	Percent
Age [years]		
Range	35–63	
Mean ± SD	47.53 ± 7.537	
Sex		
Male	19	63.3
Female	11	36.7

Table [2]: Distribution of studied sample according to risk factors

Risk Factors	Number	Percent
Diabetes Mellitus	10	33.3
Hypertension	6	20.0
Dyslipidemia	6	20.0
Family History	2	6.7
Smoking	4	13.3

Table [3]: Comparison between before and after Stem Cell Transplantation according to laboratory investigations

Variables	Stem Cell Transplantation		P value
	Before	After	
Hemoglobin [g/dL]	12.33±0.852	11.97±0.904	0.256
Sodium [mmol/L]	138.47±2.488	135.83±3.130	0.313
Potassium [mmol/L]	3.95±0.261	3.59±0.296	0.225
Troponin [ng/ml]	0.02±0.014	0.04±0.086	0.109

Table [4]: Comparison between before and after Stem Cell Transplantation according to transthoracic echocardiography findings

Variables	Stem Cell Transplantation		P value	Normal Range
	Before	After		
LVEDD [cm]	4.79±0.178	4.87±0.161	0.16	Male: 4.20– 5.84 Female: 3.78– 5.22
LVESD [cm]	3.22±0.106	3.33±0.107	0.17	Male: 2.50 – 3.98 Female: 2.16– 3.48
LVEF [%]	65.59±3.288	63.80±2.849	0.21	Male: 52– 72 Female: 54– 74
E/A	1.32±0.448	1.34±0.403	0.52	0.75–1.5
RV base [mm]	32.37±3.388	33.53±3.401	0.33	25– 41
RV mid [mm]	26.37±4.351	27.63±4.605	0.34	19– 35
RVOT at PLAX [mm]	24.87±2.529	25.90±2.808	0.21	20– 30
RVOT Proximal [mm]	26.83±2.692	27.80±2.784	0.32	21– 35
RVOT distal [mm]	22.33±2.309	23.87±2.501	0.13	17– 27
TAPSE [cm]	2.21±0.12	1.61±0.20	0.001*	2.4±0.35
Tricuspid annular S' velocity [cm/s]	14.3±2.1	9.6±2.6	0.001*	14.1±2.3
sPAP [mmHg]	20.63±1.703	22.12±2.741	0.05	>25mmHg
PAT [m/s]	143.74±8.323	141.14±9.925	0.07	> 130 m/s
RIMP [TD]	0.38 ± 0.02	0.54 ± 0.07	0.001*	0.38±0.08
RV-FAC [%]	48.93±2.463	35.73±2.947	0.009*	49±7

LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, RV: Right ventricle, RVOT: Right ventricular outflow tract, PLAX: Parasternal long axis, TAPSE: Tricuspid annular plane of systolic excursion, sPAP: systolic pulmonary arterial pressure, PAT: Pulmonary acceleration time, RIMP: Right ventricular index of myocardial performance, RV- FAC: Right ventricular Fractional area change. *: Significant P value. Normal range for every parameter following the expert's consensus: J Am Soc Echocardiogr 2014; 27:911-39

DISCUSSION

In our study, we found that TAPSE, Tricuspid annular S' and FAC showed statistically significant reduction after auto-HSCT and tissue doppler RIMP showed statistically significant increase after auto-HSCT. These results denote early RV systolic dysfunction after auto-HSCT. This was in agreement with **Tekiner *et al.*** [12] who aimed to assess echocardiographic indices in 137 patients with hematological malignancy pre-and post HSCT, among of them were 41 patients with Multiple Myeloma who had auto-HSCT. They found that no statistically significant difference observed in the left ventricular echocardiographic parameters both before and after HSCT. Furthermore, it is noteworthy to mention that there was no significant difference observed in the measurements of right ventricle [RV], right atrium, pulmonary artery pressure, pulmonary velocity, pulmonary acceleration time to pulmonary ejection time ratio [PAT/ PET], PAT, and A' velocity when comparing the pre- and post-HSCT cohorts. In comparison to the pre-transplant values, the post-transplant values of the E' velocity, S' velocity, and TAPSE exhibited a statistically significant reduction.

Our study was also in agreement with a **Tanindi A *et al.*** [13] who performed a study on 37 patients and found early subclinical reduction of RV function.

In our study, LV systolic and diastolic function and serum cTnI levels showed no statistically significant change.

Lehmann *et al.* [14] performed a study on One hundred and forty-eight patients with hematological malignancies including 18 patients with Multiple Myeloma, 96 patients underwent allogeneic grafting and 52 underwent autologous grafting. They found that HSCT procedure does not seem to affect myocardial function early after transplantation. These results are supportive to our study results.

In a study conducted by **Poręba *et al.*** [15], trans-thoracic echocardiography was employed to assess the cardiac status of 47 individuals who underwent allogeneic and auto-HSCT. The evaluations were conducted both prior to the procedure and approximately 11 days post-transplantation. The findings of this investigation revealed a decrease in left ventricular ejection fraction [LVEF], E/A ratio, and E' velocity. Conversely, an increase was observed in deceleration time [DT], isovolumetric relaxation time [IVRT], and the ratio of early diastolic trans-mitral flow velocity to early diastolic mitral annular velocity [E/E']. The findings of the study indicate the presence of initial right ventricular [RV] dysfunction, which aligns with our own findings. Additionally, early left ventricular [LV] systolic and diastolic dysfunction were observed, which are in contrast to our own results.

Roziakova *et al.* [16] conducted an assessment of the left ventricular function, highly sensitive cardiac troponin T [hs-cTnT], and N-terminal pro-B-type natriuretic peptide [NT-pro BNP] levels in patients undergoing allogeneic HSCT. The levels of hs-cTnT and NT-pro BNP exhibited a noticeable rise subsequent to the initial day of HSCT, and remained consistently elevated at the one-month mark in about one-third of the patients. Furthermore, it is noteworthy that a decline in left ventricular ejection fraction [LVEF] was observed in 13.5% of the patient cohort. Additionally, a decrease in the E/A ratio was observed in 5.4% of patients, suggesting the emergence of both systolic and diastolic dysfunction in these individuals. The findings presented herein are incongruous with the outcomes observed in our study.

In a study conducted by **Oliver *et al.*** [17], it has been demonstrated that pro-B-type natriuretic peptide [pro-BNP] exhibits an elevation in levels during hematopoietic stem cell transplantation [HSCT]. Furthermore, the assessment of global longitudinal strain [GLS] has emerged as the most specific parameter for prognosticating subclinical left ventricular dysfunction. Within the confines of the aforementioned investigation, it was observed that a notable proportion, precisely 12.5%, of the subjects exhibited a substantial decline in GLS. The findings presented herein are incongruous with the outcomes observed in our study.

Yet LV function assessment with speckle tracking to be considered in future studies as it was not locally available in our center. Additionally, new ESC guidelines mentioned that hs-cTnT has a high prognostic value for cancer treatment-related cardiac dysfunction [CTRCD] [18]. We only used conventional cTnI in our study as it was locally available. We think future studies are needed to compare sensitivity of both on CTRCT.

We suppose that chemotherapy related cardiotoxicity primarily involves RV earlier than LV. This is supported by a study performed by **Mortensen *et al.*** who performed a study on 38 patients who had hematological malignancies and were suspected with cardio-toxicity post high dose chemotherapy and 11 of them were with signs of manifest cardiotoxicity were selected for heart catheterization with endomyocardial biopsy. They found that chemotherapy related cardiac toxicity primarily involves subendocardial layer of the heart. Because RV is thinner and contains less myofibrils compared to LV, it may be more vulnerable to the toxic effects of chemo-therapeutics [19].

According to the ESMO [in 2020], the LVEF is recommended for the assessment of LV function before and after HSCT. But, in reality there are many other studies that noticed

an impairment in the RV function following chemotherapy. The low number of patients in these studies make it difficult to recommend it in practice. However, the study of "Tekiner *et al*" [published in the same year 2020] can give a plausible proof that RV function impairs earlier than the LV function. Hence, our study is another proof of concept for the earlier detection of heart failure with RV assessment.

Our study has shed lights on how useful TDI was in our study, thus clinicians could use it in clinical practice for early detection of early RV dysfunction post auto-HSCT.

Table [5]: Summarizing table of the previous studies that assessed right/left ventricle function changes before and after HSCT

Study	Number of patients	Auto/allo HSCT	Left ventricle function	Right ventricle function
The current study	30	Auto	Unchanged	Reduced but in normal range
Tekiner [12]	137	Auto/allo	Unchanged	Reduced but in normal range
Tanindi *et al.* [13]	37	-	Unchanged	Reduced but in normal range
Lehmann *et al.* [14]	148	Auto/allo	Unchanged	Not assessed
Poręba *et al.* [15]	47	Auto/allo	Reduced	Reduced but non-significant
Roziakova *et al.* [16]	37	Allo	Reduced	Not assessed
Oliver *et al.* [17]	96	Auto/Allo	Reduced	Not assessed

On the other hand, our study showed no statistically significant change in RV linear dimensions, sPAP, PAT. These results denote no evidence of early pulmonary hypertension post auto-HSCT.

This result is in agreement with **Tekiner *et al.*** [12], who found no change in sPAP, PAT and RV dimensions, and is in disagreement with a retrospective study by **Özdöver *et al.*** [20], in which their results denote elevation in sPAP with no mortality. We refer difference with this study could be because **Özdöver *et al.*** involved more patients in their study and followed up patients for longer duration.

The present study is subjected to certain limitations, which are delineated as follows: In order to ensure treatment homogeneity, our study exclusively enrolled patients who had received high-dose melphalan at a total dosage of 200 mg/m^2. Various pulmonary and cardio-vascular function parameters may exhibit associations with patient outcomes during auto-HSCT procedures employing diverse conditioning protocols. Furthermore, the measurement of Hs-cTnT and N-Terminal pro-BNP levels was not conducted in our study due to their unavailability in the local setting. Consequently, we lack information regarding the potential correlation between the deterioration of right ventricular functions and the elevation of hs-cTnT and N-Terminal pro-BNP serum levels. It is important to note that our study solely relied on the utilization of cTnI for assessment purposes. Thus, future researches are recommended to investigate the use of biomarkers, such as hs-cTnT and N-Terminal pro-BNP, to assess early cardiotoxicity post auto-HSCT. Finally, limited number of cases included in our study could be added to the overall limitation of our study. However, each patient underwent two examinations giving a total number of 60 echocardiographic examination by the same operator, but still if a large number of patients was included [probably from many centers], the result obtained would be more valuable.

Conclusion: Early right ventricular dysfunction [RVD] in patients with Multiple Myeloma post auto-HSCT, conditioned with high dose of Melphalan, is a considerable finding for researches related to cancer treatment related cardiac dysfunction [CTRCD]. Tissue doppler imaging [TDI] and TAPSE can be used as feasible measures to assess early cardiotoxicity in HSCT recipients. No evidence of significant rise in sPAP estimated by echocardiography in our study.

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