

Original Article

Effect of bone marrow transplantation on diastolic function indices

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Abstract: Introduction: High-dose chemotherapy and bone marrow transplantation result in direct and indirect changes in cardiac function. the finding suggests a decreased left ventricular diastolic compliance after high-dose cyclophosphamide treatment, but the effects of bone marrow transplantation (BMT) on cardiac diastolic function are less studied. We aimed to evaluate changes before and after the procedure in cardiac diastolic function in patients undergoing BMT. Design and methods: We designed this study to evaluate the effects of BMT on diastolic cardiac function. Patients with lymphoma (Hodgkin's and non-Hodgkin's), multiple myeloma, and solid tumors who were candidates for autologous BMT were selected for the study. The patients underwent a cardiac consultation and echocardiography before their admission for BMT. E-wave velocity and time to relaxation by tissue Doppler echocardiography in the septal, lateral, anterior, inferior, anteroseptal, and posterior wall; and the E-wave velocity of the right ventricle (RV) were measured before and after BMT. Result: Thirty patients fulfilled our inclusion criteria and entered the study. The mean diastolic function measures were calculated before and after BMT. E-wave velocity in the septal, lateral, anterior, inferior, anteroseptal and posterior walls after transplantation decreased by 19.2% ($p=0.008$), 14.5% ($p=0.008$), 22.19% ($p=0.3$), 18.9% ($p<0.001$), 21.9% ($p=0.01$), and 7.5% ($p=0.01$), respectively. The time to relaxation decreased by 13.5%, 13.7%, 12.4%, 11.4%, 11.1%, and 13.1%, respectively, after transplantation ($p<0.001$). E-wave velocity of RV decreased 15.6% after BMT ($p=0.02$). Conclusion: Data regarding alterations in diastolic functioning after BMT are scarce. This study suggests that diastolic function alters after BMT.

Keywords: Bone marrow transplantation, echocardiography, tissue Doppler

Introduction

Various cardiotoxic effects of high-dose chemotherapy and bone marrow transplantation (BMT) have been recognized in the past. A number of chemotherapy agents are known for their unfavorable effects on cardiac function. Cardiac performance can be influenced acutely, subacutely or chronically after chemotherapy.

After BMT, the most commonly encountered cardiac adverse effects include electrocardiographic changes and transient arrhythmias. Pericarditis, heart failure, pulmonary edema, and cardiac death are also less common [1, 2]. Gupta and colleagues found various cardiotoxic effects with the use of high-dose chemotherapy for conditioning before autologous BMT,

including arrhythmias, but only a small, transient decrease in left ventricular EF [3].

Highly differing rates of cardiac complications with high-dose cyclophosphamide have been reported [4]. High-dose cyclophosphamide is widely employed in transplant conditioning regimens and sequential, high-dose chemotherapy protocols for solid tumor and hematologic malignances. Although a fulminant syndrome is rare, a significant proportion of patients receiving high-dose chemotherapy were shown to have paraclinical signs of cardiotoxicity (ECG and ECHO) even without clinical findings [5, 6].

In a study by Morandi et al., the Doppler E/A mitral ratio significantly changed in two patients and were not related to fluid loading, pharmacological intervention, or heart rate variation, sug-

gesting a decreased left ventricular diastolic compliance [7].

In some cardiomyopathies, diastolic dysfunction precedes systolic dysfunction and heart failure symptoms [8].

Doppler echocardiography has become the standard method for identifying and characterizing diastolic function. Diastole encompasses the isovolumic relaxation and filling phases of the cardiac cycle and has active and passive components [9, 10].

Tissue Doppler is a new, sophisticated technique that is used to evaluate the LV filling dynamics. This technique is used to directly measure the velocity of myocardial displacement as the LV expands in diastole, in an attempt to separate the intrinsic LV contributions from those of preload.

The exact effect of BMT on cardiac diastolic function is not yet well understood. In this study, we aimed to assess the diastolic function before and after BMT using tissue Doppler echocardiography.

Materials and methods

To assess the consequences of BMT on diastolic cardiac function, we designed a before-after study. Patients with various oncologic disorders including lymphoma (Hodgkin's and non-Hodgkin's), multiple myeloma, and solid tumors who were candidates for autologous bone marrow transplantation were selected for the study. Candidacy for BMT was considered as the inclusion criteria. Patients with both normal and reduced pre BMT ejection fraction were entered the study. Patients with history of myocardial infarction, severe mitral regurgitation and severe aortic insufficiency as the cause of heart failure were excluded. The selected patients underwent a cardiac consultation and echocardiography before their admission for BMT. The same specialized echocardiographer conducted the echocardiographies with a ViVid 3 unit with the same probe and settings for all patients. For each case, the following echocardiographic diastolic function indices were measured and recorded: the tissue Doppler early diastolic Ea-wave velocity in the septal, lateral, anterior, inferior, anteroseptal, and posterior walls; the time to relaxation (duration between

beginning of Q-wave in ECG and onset of Ea-wave in TDI) in the septal, lateral, anterior, inferior, anteroseptal, and posterior walls; and the E wave velocity in free wall of the RV.

After the patient's admission to the BMT ward, mobilization with a granulocyte colony stimulating factor (GCSF) at a dose of 5mg/kg BID was given over a one-hour infusion for five days. On the sixth day, cell harvesting from the peripheral blood (apheresis) with a cell separator unit (COB brand) was performed. If the mononuclear cell count was below $4 \times 10^8/\text{kg}$, apheresis was repeated following day. When the stem cell collection was complete, the cells were maintained at 4°C, and induction chemotherapy was initiated. Lymphoma patients were treated using the CEAM regimen, which included CCNU 200mg/m², etoposide 300mg/m² for 2 days, Cytosar 300mg/m²/BID for 2 days, and melphalan 140mg/m². Multiple myeloma patients were treated with melphalan 200mg/m², and solid tumor patients were treated with ifosfamide 9g/m², carboplatin 1200mg/m² and etoposide 1500mg/m². Depending on the half-life of the prescribed chemotherapeutic agents, the harvested cells were infused 12 to 36 hours after the completion of the chemotherapy. The infusion was performed via an arrow catheter placed in the jugular or subclavian vein. One day later, GCSF 5mg/kg was initiated. After the engraftment of the white blood cells (i.e., an absolute neutrophil count ≥ 500), which usually occurs 10 to 20 days later, the patients underwent a post-BMT echocardiography. Again, the aforementioned variables assessed with the pre-BMT echocardiography were recorded.

The medical ethics committee of Shahid Beheshti Medical University approved this study. All procedures were in accordance with the Helsinki declaration, and no harm was experienced by the participants. After the data collection, SPSS statistical software, version 18, was used to analyze the raw data. A $P < 0.05$ was considered statistically significant.

Results

Thirty patients fulfilled our inclusion criteria and entered the study. Sixteen patients were male and 14 were female. Average age of participants was 43 years ranging from 17 to 61 years. Eight patients were hypertensive, 4 were

Table 1. Tissue Doppler Ea-wave in different LV walls before and after BMT

LV wall	Tissue Doppler E before BMT (cm/s)	Tissue Doppler E (after BMT) (cm/s)	Change	P value
Septal	9.31	7.52	-19.2%	0.008
Lateral	12	10.26	-14.5%	0.008
Anterior	10.68	8.31	-22.19%	0.3
Inferior	10.57	8.57	-18.9%	p<0.001
Anteroseptal	8.42	6.57	-21.9%	0.01
Posterior	12.63	11.68	-7.5%	0.01

Table 2. Time to relaxation before and after BMT

LV wall	Time to relaxation before BMT (milliseconds)	Time to relaxation after BMT (milliseconds)	Change	P value
Septal	437.74	378.58	-13.5%	p<0.001
Lateral	419.16	361.32	-13.7%	p<0.001
Anterior	430.11	376.58	-12.4%	p<0.001
Inferior	412.05	364.84	-11.4%	p<0.001
Anteroseptal	440.79	391.74	-11.1%	p<0.001
Posterior	413.47	359.11	-13.1%	p<0.001

diabetics and 6 had history of dyslipidemia. Five patients had history of smoking but at the time of study none of the patients were smoker. Ejection fraction ranged was from 41% to 60% (mean: 51%). Patients with pre BMT reduced ejection fraction were under treatment with guideline approved drugs for heart failure including beta blockers and inhibitors of angiotensin system. BMT had no significant effect on the mean blood pressure of patients at the time of follow up echocardiography and except the transient tachycardia at the time of BMT, mean pulse rate at the time of follow up echocardiography also was not changed significantly. The mean diastolic function variable measures were calculated before and after the BMT. The tissue Doppler Ea-wave mean measurements in the septal, lateral, anterior, inferior, anteroseptal and posterior walls decreased after transplantation by 19.2% (p=0.008), 14.5% (p=0.008), 22.19% (p=0.3), 18.9% (p<0.001), 21.9% (p=0.01), and 7.5% (p=0.01), respectively (**Table 1**). The most evident decrease in the tissue Doppler Ea-wave was in the anterior wall, but it was not statistically significant. The smallest decrease in the tissue Doppler Ea-wave was in the posterior wall, which was statistically significant. The time to relaxation mean measurements in the septal, lateral, anterior, inferior, anteroseptal and posterior walls decreased by 13.5%, 13.7%, 12.4%, 11.4%, 11.1%, and 13.1%, respectively, after transplantation (p<0.001). The time to relax-

ation decreased significantly in all LV walls. The most decrease in the time to relaxation was in the lateral wall, and the least decrease of this index was in the anteroseptal wall (**Table 2**). The right ventricle tissue Doppler Ea-wave mean decreased by 15.6% after the BMT (p=0.02).

Discussion

The effects of high-dose chemotherapy on cardiac systolic function have been the focus of many studies, but the alterations in diastolic function after the BMT have been studied less frequently.

In many patients with a cardiac abnormality, a diastolic dysfunction precedes a systolic dysfunction, and about 50% of patients with heart failure have diastolic heart failure. Heart failure symptoms after the BMT may be related to a diastolic dysfunction. Understanding the effects of the BMT on diastolic functioning will improve future patient management.

Zver and colleagues found that diastolic functional parameters are more sensitive predictors of early cyclophosphamide-induced cardiotoxicity. A mild, functional mitral regurgitation may develop in patients given a high-dose cyclophosphamide therapy [11].

In a study by Elbl and colleagues, high-dose chemotherapy with BMT and a medium-term

follow up did not result in any significant systolic or diastolic myocardial malfunction or decrease in cardiopulmonary performance, as compared with patients not undergoing this therapy. Treatment with the cardiotoxic medication, doxorubicin, as basic conventional chemotherapy is most likely responsible for the pathological effects in the follow-up group [12]. In a report by Hengel et al., a subacute anthracycline cardiotoxicity was described. A pulsed tissue Doppler analysis revealed low early diastolic annular velocities, consistent with diastolic dysfunction [13]. Mori et al. showed that early cyclophosphamide cardiotoxicity was characterized by LV diastolic dysfunction rather than systolic dysfunction. These findings may contribute to the acute hemodynamic deterioration observed after completing cyclophosphamide-containing conditioning chemotherapy [14].

Bu'Lock et al. examined the left ventricular (LV) diastolic function in patients previously treated with anthracycline drugs for childhood malignancy. The early diastolic filling was relatively normal or enhanced at low anthracycline doses or when fractional shortening was preserved, with a shorter isovolumic relaxation time (IVRT) and increased atrial phase filling. Early filling was reduced at higher doses or with a reduced fractional shortening, with longer IVRT and a further increase in atrial phase filling [15].

In our study, diastolic function using tissue Doppler was assessed before and after BMT. As mentioned before, the tissue Doppler Ea-wave decreased in all LV walls and in the RV. In addition, the time to relaxation decreased in all LV walls. All changes were statistically significant. A decrease in the tissue Doppler Ea-wave indicates a worsening of diastolic function, which was expected, but the decrease in time to relaxation is debatable. When the time to relaxation decreases, diastole becomes more prolonged; therefore, the blood has more time to fill the ventricles. This effect, in contrast to primary diastolic dysfunction, may enhance the LV filling and may hypothetically enhance the cardiac systolic functioning by increasing the preload (Frank-Starling mechanism).

Conclusion

We conclude that diastolic functioning worsens after BMT. However, because of an increase in

the diastolic time, the net effect may be negligible. Because our study sample was limited, future research is recommended to clarify the effects of BMT on the diastolic functioning of the heart.

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