Deformation Analysis of Myocardial Layers Detects Early Cardiac Dysfunction after Chemotherapy in Bone Marrow Transplantation Patients: A Continuous and Additive Cardiotoxicity Process

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Background: Chemotherapy-induced cardiotoxicity has not been extensively validated in bone marrow transplantation (BMT) patients. Speckle-tracking echocardiography is a sensitive method for the detection of subclinical cardiac dysfunction.

Methods: Cardiac function was prospectively assessed in 80 patients (44 men; mean age, 45 ± 11 years) after BMT for non-Hodgkin's lymphoma and acute or chronic myeloid leukemia by means of various echocardiographic techniques. Before chemotherapy for BMT, 89% of the patients had previously been treated with anthracyclines. Patients had normal left ventricular ejection fraction (LVEF). Left ventricular (LV) global longitudinal strain (GLS), subendocardial and subepicardial longitudinal strain, circumferential strain, LV twist, and right ventricular GLS were measured by speckle-tracking, and (2) three-dimensionally derived LVEF and right ventricular ejection fraction were also assessed. Abnormal LVEF was defined as <53%. Studies were performed before (baseline) and 1, 3, 6, and 12 months after chemotherapy conditioning followed by BMT.

Results: Impaired LV GLS values were observed at 1 month after chemotherapy and at 3, 6, and 12 months compared with baseline (−20 ± 2.2% at baseline, −18.4 ± 2.1% at 1 month, −17.3 ± 2.2% at 3 months, −17.1 ± 2.1% at 6 months, and −17.1 ± 2.2% at 12 months; $P = .001$). Early LV GLS changes were driven mostly by changes in subendocardial longitudinal strain (−22.5 ± 2.4% at baseline, −20.5 ± 2.3% at 1 month, −19.2 ± 2.3% at 3 months, −19.2 ± 2.4% at 6 months, and −19.1 ± 2.4 at 12 months; $P = .001$), whereas significant subepicardial strain changes were observed at 3 months after BMT. Compared with baseline, right ventricular GLS was also impaired early after chemotherapy. Compared with baseline, LVEF was slightly reduced ($P = .02$) at the end of the follow-up. Among echocardiographic markers, LV GLS at 1 month had the strongest predictive value for abnormal LVEF (<53%) at 12 months (area under the curve 0.86; 95% CI, 0.76–0.96). A cutoff LV GLS value of −18.4% had sensitivity of 84.6% and specificity of 71.9% for the identification of abnormal LVEF at the end of follow-up.

Conclusions: In BMT patients, myocardial deformation analysis detected early and progressive subclinical cardiac dysfunction. Impaired LV GLS had predictive value for the detection of abnormal LVEF at 12-month follow-up. Thus, myocardial deformation study should be applied early after BMT to prevent irreversible cardiac dysfunction by appropriate treatment. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Cardiotoxicity, Bone marrow transplantation, Speckle-tracking, 3D echocardiography

Bone marrow transplantation (BMT) has been established as the treatment of choice in a variety of hematologic and lymphoid malignancies.[1] Despite the significant improvement in survival rates,[2,3] concerns have emerged regarding early[4,5] and late[5,6] cardiovascular dysfunction after BMT, attributed partly to the use of chemotherapy before BMT.[5] Thus, early detection of cardiotoxicity

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Conflicts of Interest: None.

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Abbreviations

2D = Two-dimensional

3D = Three-dimensional

AML = Acute myeloid leukemia

BEAM = Carmustine, etoposide, cytarabine, and melphalan

BMT = Bone marrow transplantation

Bu-Thio-Flu = Busulfan, fludarabine, and thiotepa

CircS = Circumferential strain

CircSR = Circumferential strain rate

CML = Chronic myeloid leukemia

DTI = Doppler tissue imaging

GLS = Global longitudinal strain

GLSR = Global longitudinal strain rate

GLSRE = Early diastolic global longitudinal strain rate

LV = Left ventricular

LVEF = Left ventricular ejection fraction

NHL = Non-Hodgkin's lymphoma

RV = Right ventricular

RVEF = Right ventricular ejection fraction

is of crucial importance to prevent irreversible cardiac dysfunction and reduce mortality and morbidity by closer monitoring, modification of therapy, and appropriate antiremodeling treatment. Echocardiography has a central role in the noninvasive evaluation of changes in cardiac function before initiation, during, and after treatment with potentially cardiotoxic agents.[7] Cancer therapeutics–related cardiac dysfunction is commonly defined as a decrease in left ventricular ejection fraction (LVEF) by means of two-dimensional (2D) echocardiography.[7] However, LVEF is a load-dependent parameter and establishes the diagnosis of cancer therapeutics–related cardiac dysfunction in a relatively advanced stage, when impairment of heart function may be irreversible.[7-9] Assessment of myocardial deformation by means of speckle-tracking-derived strain and strain rate values is a less load-dependent and a sensitive method to detect subclinical ventricular dysfunction before LVEF is reduced in patients treated for various types of cancer.[10] Myocardial deformation analysis has been used in the setting of anthracycline- and trastuzumab-induced impairment of cardiac function[11-14] but has not been applied after chemotherapy with conditioning regimens in patients scheduled for BMT. In our study, we aimed to detect the presence of early cardiac dysfunction after treatment with chemotherapy regimens in BMT patients.

Thus, we investigated whether conventional, three-dimensional (3D) echocardiography, and deformation indices of both ventricles can detect early cardiac dysfunction resulting from the potentially cardiotoxic effects of chemotherapy in BMT, in a stepwise follow-up study.

METHODS

Study Population

We prospectively enrolled 88 patients (mean age, 45 ± 11 years; 48 men) who underwent BMT from October 2013 to December 2015 in the transplantation center of the hematologic department of the Second Propedeutic Department of Internal Medicine, University of Athens. Diagnoses included non-Hodgkin's lymphoma (NHL) in 44 patients, acute myeloid leukemia (AML) in 34 patients, and chronic myeloid leukemia (CML) in 10 patients. Before BMT, patients with NHL received conditioning therapy with BEAM (carmustine 300 mg/m^2/day for 1 day, etoposide 200 mg/m^2/day for 4 days, cytarabine 400 mg/m^2/day for 4 days, and melphalan 140 mg/m^2/day for 1 day), and patients with AML or CML received therapy with Bu-Thio-Flu (busulfan 3.2 mg/kg/day for 3 days, fludarabine 25 mg/m^2/day for 5 days, and thiotepa 5 mg/kg/day on days 5 and 6). All patients had also received chemotherapy before the decision to perform BMT and before conditioning treatment with either BEAM or Bu-Thio-Flu. Patients with NHL had received cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2 mg/m^2, and rituximab 375 mg/m^2 on day 1 and oral prednisolone 40 mg/m^2 on days 1 to 5 for six cycles and etoposide 50 mg/m^2 for 4 days, methylprednisolone 500 mg for 5 days, cytarabine 2 g/m^2 for 1 day, and cisplatin 25 mg/m^2 for 4 days for three cycles. Patients with AML had received idarubicin 12 mg/m^2 for 3 days and cytarabine 2 g/m^2 for 5 days. Patients with CML had received imatinib 400 mg/day. The mean time from initial treatment before the decision to perform BMT until administration of conditioning treatment for BMT preparation (BEAM or Bu-Thio-Flu) was 5 ± 3 months. Thus, 78 of 88 patients (89%) had received anthracyclines before chemotherapy regimens for BMT. Exclusion criteria were history of coronary artery disease (angina, ST-segment or non-ST-segment elevation myocardial infarction), atrial fibrillation, presence of wall motion abnormalities, LVEF ≤ 50%, presence of left ventricular (LV) hypertrophy on electrocardiography or echocardiography, uncontrolled hypertension, primary cardiomyopathy, and moderate or severe valvular heart disease. Ten patients with two or more risk factors for coronary artery disease underwent dobutamine stress echocardiography to exclude myocardial ischemia that could contribute to subclinical LV or right ventricular (RV) dysfunction. Patients who failed to attend one of the follow-up visit for the echocardiography study were not included in the analysis. Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

Standard Echocardiography

Echocardiography was performed before (baseline) the initiation of conditioning chemotherapy (BEAM or Bu-Thio-Flu) before BMT and 1, 3, 6, and 12 months after BMT using a Vivid 7 ultrasound system (GE Vingmed Ultrasound, Horten, Norway). All studies were digitally stored using a computerized station (EchoPAC, version 201 6.3, GE Vingmed Ultrasound, Horten, Norway) and were analyzed by two observers blinded to clinical and laboratory data. Two patients had inadequate images for analysis and thus were excluded from the study.

All measurements were performed according to the current guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[15] Interventricular septal and posterior wall thickness and LV end-diastolic and end-systolic diameters were measured. End-diastolic and end-systolic areas were measured from the apical four-chamber and two-chamber views for the calculation of LVEF using the modified biplane Simpson method. Assessment of diastolic function was based on pulsed-wave Doppler of transmitral flow, the E and A waves, and deceleration time. Doppler tissue imaging (DTI) pulsed-wave velocities were recorded from the apical four-chamber views. Mean S′ and mean E′ represent the mean systolic and mean early diastolic velocities derived from the lateral mitral annulus and basal interventricular septum, and the E/mean E′ ratio was also calculated. Midcavity transversal end-diastolic RV diameter was measured from the RV-focused four-chamber view. Markers of RV function included tricuspid annular plane