Prognostic and Added Value of Two-Dimensional Global Longitudinal Strain for Prediction of Survival in Patients with Light Chain Amyloidosis Undergoing Autologous Hematopoietic Cell Transplantation

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Background: Autologous hematopoietic cell transplantation (HCT) is a first-line therapy for prolonging survival in patients with light-chain (AL) amyloidosis. Cardiac involvement is the most important determinant of survival. However, patients with advanced cardiac involvement have often been excluded from HCT because of high risk for transplantation-related mortality and poor overall survival. Whether baseline left ventricular global longitudinal strain (GLS) can provide additional risk stratification and predict survival after HCT in this high-risk population remains unclear. The aim of this study was to evaluate the prognostic implication of baseline GLS and the added value of GLS beyond circulating cardiac biomarkers for risk stratification in patients with AL amyloidosis undergoing HCT.

Methods: Eighty-two patients with newly diagnosed AL amyloidosis who underwent upfront HCT between January 2007 and April 2014 were included in the study. Clinical, echocardiographic, and serum cardiac biomarker data were collected at baseline and 12 months following HCT. GLS measurements were performed using a vendor-independent offline system. The median follow-up time for survivors was 58 months.

Results: Sixty-four percent of patients were in biomarker-based Mayo stage II or III. GLS, brain natriuretic peptide, troponin, and mitral E/A ratio were identified as the strongest predictors of survival ($P < .0001$). Other predictors included sex, creatinine, free AL, wall thickness, and ejection fraction. Mayo stage was significantly associated with outcome, with 5-year survival of 93%, 72% and 31% in stage I, II, and III patients, respectively. GLS of 17% was identified as the value that best discriminated survivors from nonsurvivors, and the application of this cutoff value provided further mortality risk stratification within each Mayo stage.

Conclusions: GLS is a strong predictor of survival in patients with AL amyloidosis undergoing HCT, potentially providing incremental value over serum cardiac biomarkers for risk stratification. GLS should be considered as a standard parameter along with serum cardiac biomarkers when evaluating eligibility for HCT or other investigational therapies. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: AL amyloidosis, Autologous hematopoietic cell transplantation, Global longitudinal strain, Serum cardiac biomarkers, Survival

Primary or systemic light-chain (AL) amyloidosis is a rare but potentially fatal plasma cell dyscrasia characterized by tissue deposition of amyloid fibrils derived from monoclonal ALs leading to progressive organ failure.[1,2] Treatment has primarily targeted the pathologic plasma cells to terminate monoclonal AL production. First-line therapy with high-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT) has resulted in complete hematologic remission (CR) and improved 5-year survival.[3-7] Cardiac involvement occurs in 50% of cases and is the most important determinant of survival.[2,8] Troponin and N-terminal pro–brain natriuretic peptide (NT-proBNP) are sensitive and reproducible prognostic markers in AL amyloidosis. A prognostically validated Mayo staging system based on these biomarkers is commonly used for risk stratification and prediction of

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Abbreviations

2D = Two-dimensional

AL = Light chain

BNP = Brain natriuretic peptide

CR = Complete hematologic remission

GLS = Global longitudinal strain

HCT = Hematopoietic cell transplantation

LV = Left ventricular

LVEF = Left ventricular ejection fraction

NT-proBNP = N-terminal pro–brain natriuretic peptide

OS = Overall survival

TnI = Troponin I

overall survival (OS) in newly diagnosed patients undergoing frontline therapy, including HCT.[9-11] Patients are classified as stage I, II, or III on the basis of whether both NT-proBNP and troponin levels are normal, whether one biomarker is increased, or whether both are elevated, respectively. Survival decreases with each higher stage, as increasing stage correlates with the severity of underlying cardiac involvement. Patients with advanced cardiac amyloidosis classified as Mayo stage III (elevated troponin and NT-proBNP) are often not considered for HCT, because of high risk for transplantation-related mortality and poor OS.[12]

Echocardiography provides diagnostic and prognostic information in patients with AL amyloidosis suspected of having cardiac involvement.[13-18] Multiple echocardiographic parameters are predictive of outcomes. Recently, myocardial strain by two-dimensional (2D) speckle-tracking echocardiography has emerged as a highly useful tool in the evaluation of patients with cardiac amyloidosis.[19-22] Global longitudinal strain (GLS) has shown to be a strong and independent predictor of outcomes in patients with cardiac amyloidosis.[23-28] However, whether GLS is a useful marker for prognostication of survival in patients undergoing HCT independent of troponin and brain natriuretic peptide (BNP) remains unknown.

The objectives of this study were to investigate the prognostic implication of baseline (pretreatment) GLS and the added value of GLS beyond circulating cardiac biomarkers for risk stratification in patients with AL amyloidosis undergoing HCT.

METHODS

Study Population

Eighty-two patients with newly diagnosed biopsy-proven AL amyloidosis who received upfront treatment with HCT at Memorial Sloan Kettering Cancer Center between January 2007 and April 2014 were included in this study. Patients with more than two major organs involved, New York Heart Association class III or IV heart failure, or critical cardiac arrhythmias resulting in unstable hemodynamics were not eligible for HCT. Patients who received chemotherapy before HCT were excluded to eliminate any effect of prior potentially cardiotoxic exposure on baseline echocardiography and post-HCT outcomes. Hence, all baseline echocardiograms were obtained before any treatment. Clinical, laboratory, echocardiographic, and treatment data were extracted from a prospectively maintained database of an ongoing institutional review board protocol that prospectively collects baseline characteristics and outcomes of patients with systemic AL amyloidosis. One of the objectives of the protocol is to assess the prognostic value of cardiac characteristics such as laboratory and echocardiographic data in patients with AL amyloidosis receiving various types of treatment. Although the testing was performed as part of routine care, the data were prospectively collected with the intent of addressing the questions examined in the present study.

Patients were assigned a cardiac stage (mayo I, II, or III) on the basis of the cardiac biomarkers BNP and troponin.[9,29] Conversion between BNP and NT-proBNP was as follows: log BNP = 0.28 + 0.66 × log NT-proBNP; 86 pg/mO was identified as the appropriate cutoff. Stage I included patients with BNP < 86 ng/mL and troponin I (TnI) < 0.10 ng/mL, stage II included patients with either BNP ≥ 86 ng/mL or TnI ≥ 0.10 ng/mL, and stage III included patients with both BNP ≥ 86 ng/mL and TnI ≥ 0.10 ng/mL.

Echocardiography

Conventional 2D and Doppler echocardiography was performed using commercially available standard ultrasound scanners (Vivid E9 [GE Medical Systems, Milwaukee, WI] and iE33 [Philips Medical Systems, Andover, MA]), according to the standardized American Society Echocardiography protocol.[30] Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson method. Mitral inflow velocity pattern was recorded from the apical four-chamber view with the pulsed-wave Doppler sample volume positioned at the tips of the leaflets during diastole. Peak early filling (E-wave) and late diastolic filling (A-wave) velocities were measured and their ratio (mitral E/A) derived. Doppler tissue imaging of the mitral annulus was performed with measurement of the early (e′) diastolic velocity at the lateral annulus. The studies were performed following a strain protocol. Images from the apical four-chamber, two-chamber, and three-chamber views were acquired sequentially to minimize heart rate variability. Three complete cardiac cycles per loop was recorded for each view to ensure that at least one complete cycle without any truncation was available for analysis. All images were acquired during a breath hold to avoid any breathing artifacts and minimize image translation. A high-quality electrocardiographic trace was obtained to allow proper gating of the images. Settings were optimized with utmost attention paid to the image quality and resolution of the endocardial border. The depth and the sector angle were adjusted to include the left ventricle but minimizing the sector size to achieve a higher frame rate, which was maintained between 40 and 90 frames/sec. All echocardiographic images were digitally archived in Digital Imaging and Communications in Medicine format on the echocardiography information management system and retrieved offline for GLS analysis.

Myocardial Strain Measurement

GLS measurements were performed using vendor-independent offline 2D Cardiac Performance Analysis version 1.1.3 (TomTec Imaging Systems, Munich, Germany). The endocardial border was traced in end-diastole in the three apical views, which allowed the software to track myocardial movement throughout the cardiac cycle. After careful inspection, manual correction was performed if myocardial tracking was suboptimal. Each view was divided into six segments, for a total of 18 segments representing the entire left ventricle. Longitudinal strain curves were generated for each segment. GLS was calculated as the average value of the peak negative systolic strain values for all the segments within the three standard apical views. The negative nature of systolic strain or contraction can lead to confusion when describing increases or decreases in strain, as lower arithmetic value implies more vigorous contraction. For example, GLS of −20% implies better left ventricular (LV) systolic contraction but is lower in value than GLS of −14%. To avoid confusion, the normally negative GLS numbers are manually converted to positive numbers, as recommended in the