The Journal of Rheumatology

The Journal of Rheumatology **Volume 39, no. 2**

Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: If You Are Confused, Remember: "It Is a Matter of the Heart"

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J Rheumatol 2012;39;206-209
http://www.jrheum.org/content/39/2/206

Editorial

Hematopoietic Stem Cell Transplantation for Systemic Sclerosis: If You Are Confused, Remember: "It Is a Matter of the Heart"

For the past 20 years, the standard of care for systemic sclerosis (SSc) with lung involvement has been oral or intravenous (IV) cyclophosphamide (CYC). To date, there have been 2 randomized trials and 2 metaanalyses of prospective studies using oral or IV CYC in SSc-related interstitial pneumonitis (interstitial lung disease; ILD) and none have reported improvement in lung function[1,2,3,4,5]. The Scleroderma Lung Research Study Group's study in *The New England Journal of Medicine* reported that oral CYC daily for 1 year is of "modest benefit" compared to placebo[1]. However, the term "modest benefit" does not mean that lung function improved. In fact, the forced vital capacity (FVC) and DLCO declined in both placebo and CYC-treated patients[1]. "Modest benefit" means that, after 1 year, the rate of decline in FVC was less in those receiving CYC compared to placebo, but the lung function still worsened on CYC[1]. Further, at 2-year followup there was no difference in loss of lung function between oral daily CYC and placebo[2].

Due to a lack of effective standard therapy, SSc — a lethal disease that involves vital organs — needs a new and effective approach. An approach that began in patients about 14 years ago, hematopoietic stem cell transplantation (HSCT), has been demonstrated to improve both skin and lung function as well as quality of life in patients with SSc[6,7,8]. Transplantation has been performed safely in some studies[8], but results have been complicated by high treatment-related mortality in others[9]. Mortality of HSCT for SSc can be markedly reduced, however, if the reasons for mortality are properly recognized.

The safety of HSCT is determined by 3 variables: (1) the regimen (drugs) used, (2) patient selection, and (3) center effect (experience)[10,11,12,13]. It is important to recognize that the term "autologous hematopoietic stem cell transplant" is a misnomer. There is no "transplant," only the infusion of an autologous blood product: autologous HSCT is analogous to a surgeon collecting before, and then reinfusing autologous packed red blood cells, after an operation. The toxicity from the regimen depends upon the specific drugs. The toxicity and risk of total body irradiation is different from the toxicity of antithymocyte globulin (ATG), which is different from the toxicity of rituximab, which is different from the toxicity of busulfan, which is different from the toxicity of CYC, etc. However, if autologous stem cells are given as a supportive blood product after any of these drugs and then termed "transplant," there is a tendency to subsequently construe all transplant risk and morbidity as identical. This perception is unintentionally perpetuated by investigators in the field, because it has been common for trials using different regimens (with different toxicities) and performed independently at different centers under different standard of care guidelines to be published together and then republished later with other centers and larger numbers of patients. When evaluating the literature, it is difficult to determine how many patients are being re-reported and how much toxicity to attribute to different regimens utilized.

It is, at least in terms of safety, important for the reader to differentiate whether the transplant regimen is myeloablative or nonmyeloablative[10,11]. Before receiving a transplant, patients with autoimmune diseases receive a "conditioning regimen" of drugs (chemotherapy, biologics, and/or radiation) that destroys lymphocytes, inducing an immediate immune ceasefire. Subsequently, HSC are infused to regenerate a new immune system that defaults to self-tolerance in the noninflammatory postconditioning environment (in immunologic vernacular, no costimulation). Extreme conditioning regimens that cause irreversible bone marrow failure, thus requiring mandatory HSC reinfusion, are termed myeloablative and contain agents such total body irradiation that also substantially increase the risk of late leukemia, myelodysplasia, and solid tumors. In contrast, nonmyeloablative regimens are less extreme and consist of relatively lymphocyte-specific chemotherapy (CYC or fludarabine) and antilymphocyte antibodies (e.g., ATG, rituximab) that halt inflammation without altering the bone mar-

See Optimization of autologous stem cell transplantation for SSc, *page 269*.

row's ability to recover; they are safer, with less short and longterm toxicity[10,11].

In this issue of *The Journal*, Henes, *et al* report a high mortality despite using a nonmyeloablative regime[14]; in their report mortality was predominately cardiovascular, which takes us to the second important factor for low transplant morbidity: patient selection. SSc is a unique disease in terms of pretransplant cardiac evaluation because an extensive precardiac evaluation to exclude pulmonary arterial hypertension (PAH) and primary SSc cardiac and pericardial involvement is essential for low transplant-related mortality.

For most diseases, echocardiogram as prescreening evaluation before transplant is sufficient. For SSc, however, routine echocardiogram by itself, especially without adequate right ventricular assessment, is insufficient. Echocardiographic measurement of pulmonary artery systolic pressure (PASP), commonly used to assess PAH, is a calculated value based upon measured tricuspid valve regurgitant velocity (TRV)[15], which is used to calculate PASP according to the modified Bernoulli pressure/velocity equation[16] ($P = 4v^2$), i.e., $PASP = 4(TRV)^2$. Although there is a high correlation (0.57 to 0.93) between PASP measured by echocardiography and right heart catheterization[17], echocardiographic PASP can significantly over- or underestimate invasive PASP, due to problems with image quality, Doppler alignment, and violation of viscosity assumptions in the modified Bernoulli equation. For patients with SSc, therefore, we perform right heart catheterization to confirm PASP; and for the echocardiogram, we include measurement of right ventricle tricuspid annular plane systolic excursion (TAPSE). TAPSE is the maximal distance that the triscuspid annulus moves between systole and diastole. The lower the TAPSE value, the greater the impairment of right ventricular contractility. Since TAPSE < 1.8 cm is prognostic for high PAH-related mortality[18], TAPSE < 1.8 cm should be considered a contraindication for HSCT.

Right heart catheterization is considered the gold standard to rule out PAH defined as a mean pulmonary artery pressure (mPAP) > 25 mm Hg[16]. Thus, we exclude patients with a PASP > 40 mm Hg or mPAP > 25 mm Hg measured by right heart catheterization. However, using a normal pulmonary artery pressure as sole transplant exclusion criterion may be falsely reassuring because the relationship between pulmonary vascular resistance (PVR), mPAP, pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) is defined by PVR = (mPAP – PCWP) x 80)/(CO). A failing right ventricle will result in a decreased cardiac output that will decrease or even normalize pulmonary artery pressure; but the PVR (as the ratio of mPAP/CO) will remain elevated. In patients with SSc who have PAH and/or direct cardiac involvement, PAP is also volume-dependent, and at the time

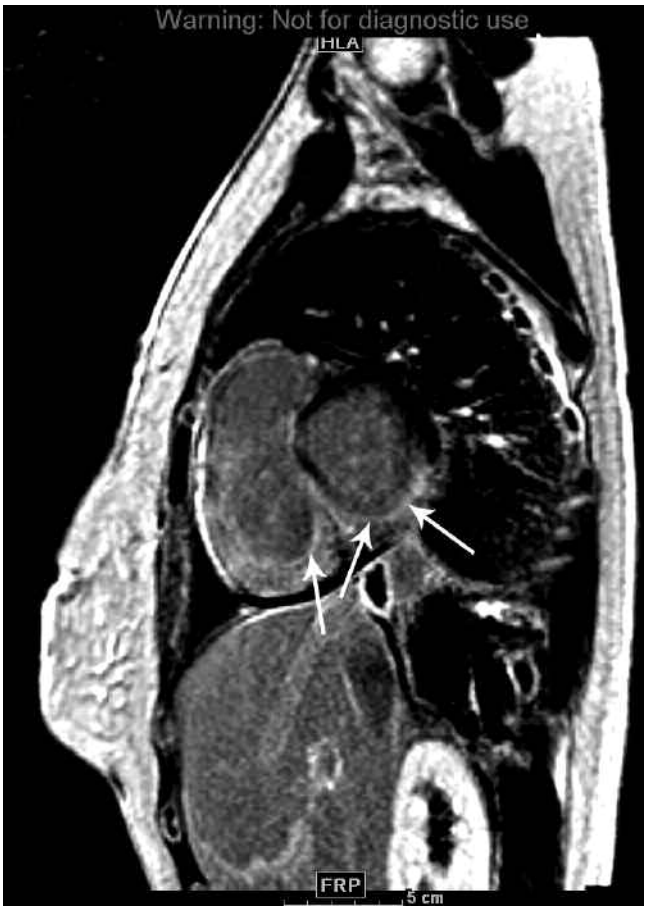

Figure 1. Magnetic resonance short axis view delayed post-gadolinium image demonstrating inferior left and right ventricular intramyocardial enhancement (fibrosis; arrows).

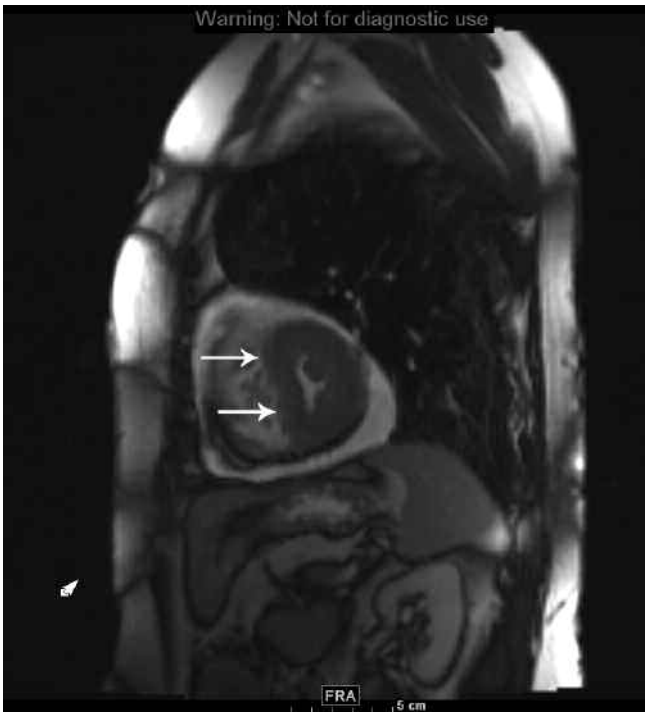

Figure 2. Magnetic resonance imaging short axis view demonstrating intraventricular diastolic flattening (D-sign; arrows).

of measurement, patients may be relatively volume-depleted, having been NPO since the previous night. It is important to recognize that values obtained during right heart catheterization must be interpreted in context, not in isolation.

Constrictive pericarditis, another SSc-related cardiac complication — and a contraindication for HSCT — can also be evaluated using a combination of right heart catheterization, echocardiography, and cardiac magnetic resonance imaging (MRI; see below). For clinical suspicion of SSc-related occult constrictive pericarditis (dyspnea on exertion out of proportion to pulmonary function test values), right and left cardiac catheterization with a fluid challenge (1000 cc bolus of normal saline over 10 minutes) may be required for diagnosis[19].

In addition to performing echocardiogram with right ventricular assessment (TAPSE) and right heart catheterization, we also prescreen patients with SSc by cardiac MRI for assessment of ventricular volumes and function and inflammation and/or fibrosis[20]. In Figure 1 cardiac MRI performed on a patient 18 years of age with a 24-month history of SSc who was excluded from HSCT despite normal right heart catheterization shows extensive intramyocardial fibrosis that increases risk of arrhythmias[21]. Figure 2 shows the cardiac MRI of a patient excluded from HSCT despite normal PASP because of a failing right heart as demonstrated by intraventricular diastolic flattening (D-sign) and elevated PVR.

Questions regarding optimal cardiac screening and exclusion criteria for patients with SSc will require further study. However, transplant morbidity and mortality is significantly reduced by proper patient selection. Based on experience from ASSIST I[8], exclusion criteria for the randomized ASSIST II trial (www.clinicaltrials.gov NCT NCT01445821) include PAH (PASP > 40 mm Hg, mPAP > 25 mm Hg), cardiac dysfunction (TAPSE < 1.8 cm, significant intraventricular diastolic flattening, intramyocardial fibrosis), and pericardial disease (pericardial effusion > 1 cm, constrictive pericarditis). Since standard therapies do not decrease the risk of subsequent cardiac involvement that would preclude a safe transplant, HSCT should not be viewed as a salvage option, but instead considered upfront as initial therapy at a time when it can be performed safely for either diffuse SSc or limited cutaneous SSc with ILD.

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J Rheumatol 2012;39:206–9; doi:10.3899/jrheum.111302