Cardiac Assessment Before Stem Cell Transplantation for Systemic Sclerosis

To the Editor The key to safe hematopoietic stem cell transplantation in patients with systemic sclerosis is a careful pretransplant cardiac assessment and subsequent recognition and management of cardiac complications.[1] In the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial by Dr van Laar and colleagues,[2] the main exclusion criteria for cardiac reasons were left ventricular ejection fraction less than 45% and pulmonary arterial hypertension, defined as a mean pulmonary artery pressure greater than 50 mm Hg by echocardiogram or cardiac catheterization.

There are 2 problems with this definition. First, the accepted definition of pulmonary arterial hypertension is a mean pulmonary artery pressure of 25 mm Hg or greater on invasive hemodynamic testing.[3] Second, an echocardiogram cannot reliably determine mean pulmonary artery pressure (echocardiography typically estimates pulmonary artery systolic pressure), and in patients with pulmonary arterial hypertension, there is poor correlation between pulmonary artery systolic pressure by echocardiography and mean pulmonary artery pressure by invasive testing.[4] Regardless of what each of the 29 centers did in terms of cardiac evaluation, these criteria were not adequate for exclusion of pulmonary arterial hypertension.

Systemic sclerosis may cause intrinsic myocardial ischemia and fibrosis (from cardiac microvascular disease), left ventricular diastolic dysfunction, and pericardial disease (including constrictive pericarditis).[5] In patients with systemic sclerosis and restrictive or constrictive cardiac physiology, left ventricular ejection fraction is typically normal and falsely reassuring because these patients are likely to develop pulmonary edema, multiorgan dysfunction in the setting of hematopoietic stem cell transplantation, or both, precipitated by cardiovascular stressors such as fever or volume overload. This may result, as in the ASTIS trial, in erroneous misdiagnoses of cardiac-related deaths as pulmonary edema, multiorgan failure, or even sepsis.

The treatment-related mortality rate of 10% in the transplant group of the ASTIS study was likely attributable to the use of cancer-specific cardiac screening. Systemic sclerosis has unique and complex cardiac manifestations that require disease-specific screening and management, including echocardiography with tissue Doppler and quantitative assessment of right ventricular function (eg, tricuspid annular plane systolic excursion), right heart catheterization with fluid challenge, and cardiac magnetic resonance imaging with gadolinium contrast (including T1 mapping for assessment of diffuse myocardial fibrosis), as have been developed in the American Scleroderma Stem Cell vs Immune Suppression Trial (ASSIST).[1]

Richard K. Burt, MD
Maria Carolina Oliveira, MD
Sanjiv J. Shah, MD

Author Affiliations: Division of Immunotherapy, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Burt); Division of Clinical Immunology, University of São Paulo, Ribeirão Preto, Brazil (Oliveira); Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah).

Corresponding Author: Richard K. Burt, MD, Division of Immunotherapy, Northwestern University Feinberg School of Medicine, 446 E Ontario, Chicago, IL 60611 (rburt@northwestern.edu).

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In Reply Dr Burt and colleagues emphasize the importance of extensive cardiopulmonary screening before undertaking autologous hematopoietic stem cell transplantation in patients with severe systemic sclerosis. When the ASTIS trial was launched in 2001, phase 1/2 data indicated that patients with systemic sclerosis and a mean pulmonary arterial pressure greater than 50 mm Hg measured by right heart catheterization had an unacceptable risk of treatment-related mortality[1] and were therefore excluded from the ASTIS trial.

Cardiac screening of all ASTIS candidates was mandatory following the 2004 European Group for Blood and Marrow Transplantation consensus statement[2] in which right heart catheterization was performed if the cardiac echocardiographic estimation of systolic pulmonary pressure was greater than 40 mm Hg. This does not fully exclude pulmonary arterial hypertension as Burt and colleagues point out, but at the time was considered adequate to exclude those patients likely to have a mean pulmonary artery pressure greater than 50 mm Hg. All patients with an echocardiographic estimation of systolic pulmonary pressure greater than 40 mm Hg were further evaluated by right heart catheterization, and none had a mean pulmonary artery pressure of greater than 50 mm Hg. New 2009 guidelines on pulmonary arterial hypertension, which redefine it as a mean pulmonary artery pressure greater than 25 mm Hg, have allowed earlier recognition and more comprehensive assessment of cardiopulmonary involvement in systemic sclerosis.[3]

Burt and colleagues are correct in stating that extreme caution is required regarding cardiac screening in such patients to assess treatment-related risk from pulmonary arterial hypertension, primary cardiac involvement, or pericardial disease; new knowledge since the ASTIS trial commenced 12 years ago has allowed further refinement of screening.[4]

We agree with Burt and colleagues that it is sometimes difficult to determine the exact cause of death in the complex setting of multiorgan failure and that cardiac causes may have been underdiagnosed. However, the conclusions of the independent data and safety monitoring committee based on the investigators' data were binding.

In-depth subgroup analyses are under way to further refine the protocol for patient selection and monitoring, with the aim of reducing treatment-related mortality to less than the 10% seen in the ASTIS trial. Exclusion of patients with less severe pulmonary arterial hypertension may be indicated, although no signal of harm in such patients emerged in assessments by the independent data and safety monitoring committee during the trial.

However, some degree of treatment-related mortality will always be associated with hematopoietic stem cell transplantation in a severe disease such as systemic sclerosis, in which progression is associated with poor survival.[5] It is gratifying that in ASSIST, no treatment-related mortality occurred in 17 transplanted patients; however, the first treatment-related death in the ASTIS trial occurred after 28 transplants, emphasizing the importance of large clinical trials.

Jacob M. van Laar, MD, PhD
Dominique Farge, MD, PhD
Alan Tyndall, MD

Author Affiliations: Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, the Netherlands (van Laar); Assistance Publique-Hôpitaux de Paris, Saint-Louis Hospital, Paris, France (Farge); Department of Rheumatology, University Hospital Basel, Basel, Switzerland (Tyndall).

Corresponding Authors: Jacob M. van Laar, MD, PhD, Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, the Netherlands (j.m.vanlaar@umcutrecht.nl); Dominique Farge, MD, PhD, Saint-Louis Hospital, Paris 7 University, 75010 Paris, France (dominique.farge-bancel@sls.aphp.fr).

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Additional Information: Drs van Laar and Farge contributed equally.

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Ethical Considerations Surrounding Lethal Injection

To the Editor Perhaps no part of the criminal justice system is more fraught with moral, ethical, and legal dilemmas than the execution process. The paramount concern of the Death Penalty Committee of The Constitution Project was to ensure that the system is as fair and transparent as possible and comports with the numerous protections found in the US Constitution. As Dr Truog and colleagues[1] pointed out, the Committee of The Constitution Project found that the justice system fails to do this in many areas and made recommendations to address these failures in its report.[2]

In the last pages of the report,[2] the Committee addressed what is known to be a recurring problem in the death penalty process: untrained, ill-equipped individuals conducting the error-prone procedures involved in lethal injection, resulting in unconstitutional executions. To be sure, the Committee does not endorse a particular method of execution, but in jurisdictions that use lethal injection to kill prisoners, the report provided minimum safeguards that must be in place to prevent undue pain and suffering in accordance with the Eighth Amendment. If these dictates cannot be met in any particular execution process whether by lethal injection or some other method, then it should not be carried out.

The members of the Committee are not medical ethicists. The recommendations leave the important ethical considerations to those who practice medicine and relevant governing bodies. In the report,[2] the Committee affirmed that, "Doctors and other medical professionals should not be compelled to violate medical ethics. The result may be that medical professionals will not be able to be present for executions…"

If the consensus is as Truog and colleagues[1] stated that no medical personnel could ever ethically participate in any part of the execution process, then that is the end of the inquiry. However, it was noted in the Viewpoint that at least one physician (and probably more) believes medical personnel participation is ethical. This is a question for the medical community to determine, and the Committee respects that process, regardless of how it might affect the availability of lethal injection.

If medical professionals are ethically barred from participating in executions, the responsibility for finding a method of execution that does not violate the Eighth Amendment, along with myriad other problems identified in the report,[2] lies at the feet of policy makers.

Mark White, JD

Author Affiliation: The Constitution Project, Washington, DC.

Corresponding Author: Mark White, JD, The Constitution Project, 1200 18th St NW, Washington, DC 20036 (smclean@constitutionproject.org).

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In Reply The report[1] by the Committee of The Constitution Project correctly states that "Doctors and other medical professionals should not be compelled to violate medical ethics," and former Governor White adds that if there is indeed consensus