Systemic Sclerosis Stem Cell Transplant Risky but Promising

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Autologous hematopoietic stem cell transplantation (HSCT) can produce durable event-free survival for patients with diffuse cutaneous systemic sclerosis (SSc) who are able to survive the procedure, but the type of pretransplant cardiac workup commonly used with HSCT in oncology is not sufficient to identify those who are unlikely to survive HSCT long enough to benefit, according to a new study published online June 24 in *JAMA*.

Coauthor Alois Gratwohl, MD, told *Medscape Medical News*, "There is now a treatment modality available for patients with severe systemic sclerosis, which can alter the devastating natural course of the disease. HSCT should be envisaged very early on; HSCT cannot change already-existing irreversible organ damage." Dr. Gratwohl is professor emeritus, former head of hematology, and former head of the stem cell transplantation team, Basel University Hospital, Switzerland.

Short-term Risk, Long-term Gain

The phase 3 Autologous Stem Cell Transplantation International Scleroderma (ASTIS) open-label, parallel-group trial included 29 clinical centers in 10 countries. The researchers, led by Jacob M. Van Laar, MD, PhD, from the Department of Rheumatology and Clinical Immunology, University Medical Center, Utrecht, the Netherlands, enrolled 156 patients with early diffuse cutaneous systemic sclerosis. The reserchers randomly assigned patients either to HSCT (n = 79) or to standard treatment with cyclophosphamide (n = 77) between 2001 and 2009 and followed them up until October 31, 2013.

For patients randomly assigned to receive HSCT, peripheral blood hematopoietic stem cells were mobilized with intravenous cyclophosphamide (a total of 4 g/m^2 administered in equal amounts on 2

consecutive days) and filgrastim (10 µg/kg per day), harvested by leukapheresis, and enriched for CD34+ cells, using immunomagnetic separation. The conditioning regimen was cyclophosphamide (200 mg/kg intravenously over the course of 4 consecutive days) and intravenous rabbit antithymocyte globulin (a total of 7.5 mg/kg administered in equal amounts over the course of 3 consecutive days) administered with intravenous methylprednisolone (1 mg/kg) and hyperhydration, followed by reinfusion of peripheral blood autologous CD34+ stem cells ($\geq 2 \times 10^6$/kg). The control group received 12 monthly pulses of intravenous cyclophosphamide (750 mg/m^2).

This approach is based on the idea that using a nonmyeloablative conditioning regimen to destroy the patient's self-reactive lymphocytes and then infusing autologous hematopoietic stem cells can regenerate a new immune system and restore self-tolerance.

The study's primary end point was event-free survival, which the researchers defined as the time in days from randomization until the occurrence of death from any cause or persistent major organ failure.

During a median follow-up of 5.8 years, there were a total of 53 events: 22 in the HSCT group (19 deaths and 3 irreversible organ failures) and 31 in the control group (23 deaths and 8 irreversible organ failures). During the first year, more events occurred in the HSCT group (13 events [16.5%], including 8 treatment-related deaths) than in the control group (8 events [10.4%], with no treatment-related deaths). At 2 years, the HSCT group experienced 14 events (17.7%) vs 14 events (18.2%) in the control group. At 4 years, a total of 15 events (19%) had occurred in the HSCT group vs 20 events (26%) in the control group. At 4 years, time-varying hazard ratios (modeled with treatment × time interaction) for event-free survival were 0.35 (95% confidence interval, 0.16 - 0.74) and 0.34 (95% confidence interval, 0.16 - 0.74) at 2 years.

The researchers also found that HSCT was more effective than cyclophosphamide on measures evaluating skin, functional ability, quality of life, and lung function.

Fluid Challenge Is Key for Reducing Treatment-Related Deaths

Richard K. Burt, MD, who recently reported his experience with HSCT in more than 90 patients with SSc, told *Medscape Medical News* that the ASTIS trial both highlights the "miserable" outcomes for current standard care in severe SSc (mortality, 6% - 7% per year) and illustrates the importance of thorough pretransplant cardiac evaluation. Dr. Burt, who was not involved in the study, is chief, Division of Medicine-Immunotherapy and Autoimmune Diseases, Northwestern University Feinberg School of Medicine, Chicago, Illinois.

In Dr. Burt's retrospective series, treatment-related posttransplant mortality was only 6% vs more than 10% in the ASTIS study. "To some extent, that reflects the fact that the ASTIS trial was done between 2001 and 2009, before there was greater understanding of how to select patients for HSCT," Dr. Burt said.

Current treatment-related post-HSCT mortality at Dr. Burt's center is less than 5%, which he attributed to

better patient selection (based on cardiac evaluation) and to a growing understanding that adding fluids is generally a mistake in patients with scleroderma, whether or not they have had HSCT.

The main tool for judging cardiac fitness for HSCT in the ASTIS study was cardiac echocardiography, following the practice in oncology HSCT. Some patients also had catheterization of the right side of the heart.

Tight Skin = Tight Ventricle

Dr. Burt said that achieving 5% treatment-related mortality requires thorough screening of the heart, using fluid challenge with cardiac catheterization (to detect pulmonary hypertension, constriction, or left ventricular diastolic dysfunction) and cardiac magnetic resonance imaging with gadolinium, as well as echocardiography.

"Those examinations will tell you whether it is too late to attempt HSCT for a particular patient," Dr. Burt said. "If there is too much stiffness in the left ventricle, if there is a D-sign (intraventricular diastolic flattening on [magnetic resonance imaging]), proceeding with HSCT is too dangerous and should not be attempted."

"Tight skin means tight left ventricle and signals the need to be very careful with fluids," Dr. Burt said. "Scleroderma patients get into trouble 3 ways: pulmonary hypertension, pericardial constriction, and a stiff, noncompliant left ventricle due to microfibrosis in the ventricle itself. All of those problems have to be managed by avoiding fluids, whether you do a transplant or not. It is common in cancer care to hyperhydrate patients. If you do that in scleroderma patients, you are going to get into trouble."

According to Dr. Burt, a tight, noncompliant left ventricle (even with a normal ejection fraction) is vulnerable to stress, such as fever or fluid, which goes back to the lungs as pulmonary edema, causing the patient to become tachycardic. "Unfortunately, less-experienced clinicians or emergency room personnel may mistake this for sepsis and run fluids, which makes the cycle worse. With scleroderma patients, you don't run fluids, you give them diuretics," Dr. Burt said.

In an accompanying editorial , Dinesh Khanna, MD, from the University of Michigan, Ann Arbor, and colleagues suggest that HSCT be reserved for patients with SSc who have diffuse cutaneous systemic sclerosis within the first 4 to 5 years of onset with mild-to-moderate internal organ involvement or limited cutaneous SSc with progressive internal organ involvement, who have failed to improve or have worsened on conventional immunosuppressive therapy, and who are not active smokers.

Dr. Gratwohl disagreed somewhat with these recommendations. "Who will profit most from HSCT remains the crucial question. General feelings tend to suggest that HSCT should be reserved for those who failed conventional therapy, but this might be wrong. A subgroup analysis indicates that nonsmokers fared

much better with HSCT, without the early mortality. It will be most crucial to define patients at highest risk for severe disease and to treat them with HSCT very early on," he said.

Dr. Gratwohl has disclosed no relevant financial relationships. Various coauthors report having various financial relationships with Genentech, Roche, Menarini, Bristol-Myers Squibb, Abbott, Novartis, Miltenyi, Tigenix, Pfizer, Actelion, Therabel, United Therapeutics, Abbvie, UCB, Merck Sharp & Dohme, Deutsche Forschungsgemeinschaft and Bundesministerium für Bildung und Forschung, Baxter, GlaxoSmithKline, CSL Behring, the American Academy of Allergy, Asthma, and Immunology, Amgen, Chugai, Janssen, Galapagos, and Imtex-Sangstat. Dr Khanna reported receiving grants from the Scleroderma Foundation, Pulmonary Hypertension Association, and the National Institutes of Health during the conduct of the study and receiving personal fees from Actelion; receiving grants and personal fees from Bristol-Myers Squibb; receiving personal fees from Biogen Idec, DIGNA, GlaxoSmithKline, Genentech/Roche, InterMune, Merck/EMD Serono, sanofi aventis/Genzyme, and Bayer, outside the submitted work. One coauthor has reported receiving honoraria from Therakos and Merck, outside the submitted work. Dr. Burt has disclosed no relevant financial relationships.

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