Stem cell transplantation for severe sclerosis associated with improved long-term survival

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Among patients with a severe, life-threatening type of sclerosis, treatment with hematopoietic stem cell transplantation (HSCT), compared to intravenous infusion of the chemotherapeutic drug cyclophosphamide, was associated with an increased treatment-related risk of death in the first year, but better long-term survival, according to a study in the June 25 issue of *JAMA*.

Systemic sclerosis is an autoimmune connective tissue disease characterized by vasculopathy (a disorder of the blood vessels), low-grade inflammation, and fibrosis (development of excess fibrous connective tissue) in skin and internal organs. Previously, small studies have shown that systemic sclerosis is responsive to treatment with autologous HSCT, although it has been unclear whether HSCT improves survival, according to background information in the article. For this study, autologous HSCT involved a multistep process beginning with infusion of high doses of cyclophosphamide and an antibody against immune cells, followed by reinfusion of the patient's own stem cells that had been previously collected from blood and purified.

Jacob M. van Laar, M.D., Ph.D., of the University Medical Center Utrecht, Utrecht, the Netherlands and Dominique Farge M.D., Ph.D, of the Assistance Publique - Hopitaux de Paris, Paris 7 Diderot University, France, and colleagues randomly assigned 156 patients with early diffuse cutaneous (widespread skin involvement) systemic sclerosis to receive HSCT (n = 79) or cyclophosphamide (n = 77; 12 monthly infusions). The phase 3 clinical trial was conducted in 10 countries at 29 centers;

patients were recruited from March 2001 to October 2009 and followed up until October 2013.

During a median follow-up of 5.8 years, 53 adverse events occurred: 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). Patients treated with HSCT experienced more adverse events (including death) in the first year but had better long-term event-free survival than those treated with cyclophosphamide.

Patients in the HCST group experienced higher mortality in the first year but had better long-term overall survival than those treated with cyclophosphamide. During year 1 there were 11 deaths (13.9 percent, including 8 treatment-related deaths) in the HSCT group vs 7 (9.1 percent, no treatment-related deaths) in the control group. After year 2 of follow-up, there were 12 deaths (15.2 percent) in the HSCT group vs 13 (16.9 percent) in the control group. After 4 years of follow-up, there were 13 deaths (16.5 percent) in the HSCT group vs 20 (26.0 percent) in the control group.

The authors add that HSCT was also more effective than intravenous cyclophosphamide on measures evaluating skin, functional ability, quality of life, and lung function, consistent with previous studies.

"Among patients with early diffuse cutaneous systemic sclerosis, HSCT was associated with increased treatment-related mortality in the first year after treatment. However, HCST conferred a significant long-term event-free survival benefit," the authors conclude.

In an accompanying editorial, Dinesh Khanna, M.D., M.Sc., of the University of Michigan, Ann Arbor, and colleagues provide suggestions on which patients should receive HSCT.

"Currently, consideration should be limited to patients with (1) diffuse cutaneous systemic sclerosis within the first 4 to 5 years of onset with mild-to-moderate internal organ involvement (severe internal organ involvement will make patients ineligible because of risks associated with HSCT) or (2) limited cutaneous systemic sclerosis with progressive internal organ involvement. This consideration also should generally be restricted to patients who have failed to improve or have worsened on conventional immunosuppressive agents and who are not active smokers; … Last, the cost-effectiveness of HSCT needs to be established, and multidisciplinary models of treatment decision making coupled with patient decision tools are needed. These approaches will provide a framework to evaluate and understand the trade-off between long-term benefits and short-term treatment-related morbidity and mortality of HSCT in patients with systemic sclerosis."

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