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CONNECTIVE TISSUE DISEASES

Stem cell transplant prolongs systemic sclerosis survival

12-year multicentre clinical trial data now reported in *JAMA* show haematopoietic stem cell transplantation (HSCT) has long-term survival benefits compared with pulsed cyclophosphamide for treating systemic sclerosis (SSc). "No therapy has previously been shown to improve long-term survival," say corresponding authors of the study, Jaap van Laar and Dominique Farge-Bancel, "particularly for those patients with diffuse cutaneous SSc and organ involvement."

The investigator-initiated Autologous Stem Cell Transplantation International Scleroderma (ASTIS) clinical trial began as a European Group for Blood & Marrow Transplantation collaboration with EULAR in the wake of data showing HSCT can improve functional ability and reduce lung, skin and vascular pathology in patients with SSc.

From 2001–2009, patients ($n = 156$) with diffuse cutaneous SSc were recruited from 29 centres in 10 different countries for the open label phase III study. Patients were randomized to receive either HSCT ($n = 79$) or 12 monthly intravenous injections of pulsed cyclophosphamide ($n = 77$).

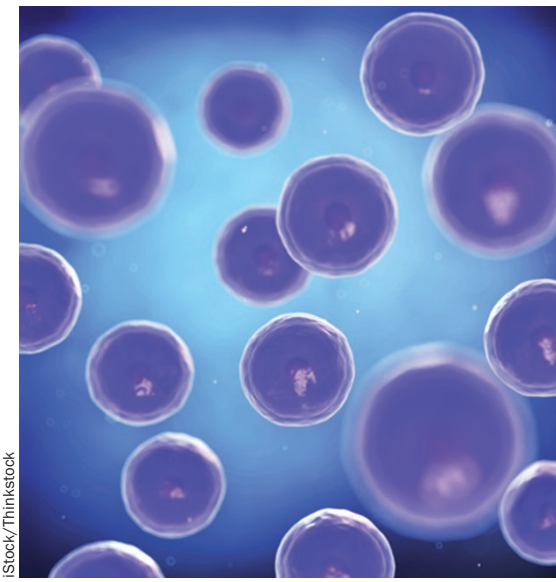
HSCT involved intravenous injection of filgrastim and cyclophosphamide on two consecutive days before isolation of $CD34^+$ cells from the blood. In preparation for reinfusion of $\geq 2 \times 10^6$ of these stem cells, patients were conditioned with cyclophosphamide, antithymocyte globulin, methylprednisolone and hyperhydration.

Switching therapies was prevented for two years, patients were followed-up until 2013, and the primary endpoint was 'event-free survival', a term Alan Tyndall, senior author of the study, defines as "time in days from randomization until either death from any cause or precisely defined persistent endstage major organ failure, such as heart, lung or kidney failure."

"In some patients a complete response was seen, including normalization of skin and loss of all autoantibodies," say the authors. In the first year after treatment there were 13 adverse events in the HSCT group (16.5%, including 8 deaths) and 8 in the control group (10.4%, no deaths). By contrast, after a median follow-up of 5.8 years there were 22 adverse events in the HSCT group (19 deaths, 3 irreversible organ failures) and 31 in the control group (23 deaths, 8 irreversible organ failures).

These data highlight the importance of long-term trials. "Other studies have shown that if a trial was stopped too soon we would not have known the full risk versus benefit," comments Janet Pope, an independent SSc expert at the University of Western Ontario. "A famous example," she continues "is the tight control for type 1 diabetes mellitus trial."

Although the ASTIS results are positive, Pope notes "this treatment only applies to patients with early diffuse cutaneous SSc who are at risk of doing poorly." However, she says this is a "landmark study" as it might mean "we can find a cocktail treatment with less immune ablation and morbidity to help many more of our patients."



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Original article van Laar, J. M. *et al*. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis. *JAMA* doi:10.1001/jama.2014.6368