Autologous HSCT in systemic sclerosis: a step forward

Early and rapidly progressive systemic sclerosis with skin or internal organ involvement, predominantly of the lung, is associated with 3–5-year survival of 50–80%. In the past decade, despite improved screening for systemic sclerosis and new drugs for pulmonary hypertension, no treatment has been effective for the 10–20% of patients with life-threatening disease. After the first use of haemopoietic stem-cell transplantation (HSCT) for systemic sclerosis in 1997, several phase 1 and 2 studies of autologous HSCT for systemic sclerosis reported encouraging results with rapid and durable decreases in skin score, improved functional status, stable lung function, and effective regression of fibrosis on skin histology and lung imaging. Although transplantation-related mortality decreased to 3–5%, an effect related to activity at a specific centre was noted. Three randomised trials with similar eligibility criteria and control groups were then undertaken, either with non-myeloablative regimens (cyclophosphamide and rabbit antithymocyte globulin) with CD34-positive selection for the European multicentre Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial, without CD34-positive selection for the American single-centre ASSIST trial, or a total body irradiation myeloablative regimen for the US multicentre Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial. Recruitment in these trials is challenging, because systemic sclerosis is a rare autoimmune disease (prevalence 7–50 per million) and HSCT is a well-validated procedure rather than a new drug. Little support was thus given to this innovative therapeutic approach, which can indeed reset the immune response.

The results of Richard Burt and colleagues’ ASSIST study in the Lancet provide the best data to date for transplantation in scleroderma. Nonetheless, we await the findings from the ongoing phase 3 trials: ASTIS had completed enrolment of 156 patients in 2009, whereas SCOT is still recruiting. ASSIST, a randomised phase 2 trial, showed for the first time the short-term clinical superiority of HSCT in ten patients with systemic sclerosis by substantial regression of modified Rodnan skin score, a strong predictor of outcome, and of volume of pulmonary disease on high-resolution chest CT plus improved functional status on short-form (SF-36) score, whereas nine patients who were given cyclophosphamide (six intravenous boluses every month) progressed or did not improve by 1 year. This trial, originally designed to enrol 60 patients, allowed crossover for the eight control patients who progressed, of whom seven with no contraindication switched to HSCT. All 17 participants who received HSCT without transplant-related mortality improved, with a follow-up of at least 2 years for 11 patients. Nonetheless, stopping rules for significant differences in outcome between the two groups allowed early discontinuation of the trial. Failure to achieve equipoise solved the ethical issue of sustained randomisation in this single-centre study at Northwestern Memorial Hospital (Chicago, IL, USA).

10 years ago, when these trials were designed, patients with severe systemic sclerosis were offered investigational HSCT as part of an ethical approach that was of increased risk but expected to achieve improved results compared with 6 or 12 months of intravenous cyclophosphamide, the best available therapy. However, meta-analysis of observational and randomised studies undertaken since then showed that oral or intravenous cyclophosphamide did not affect the mean difference of forced vital capacity or diffusion capacity of carbon monoxide after 12 months of therapy, or alter the risk of adverse events (as in the ASSIST control group). Random allocation of patients to a therapy known not to be beneficial (cyclophosphamide) is therefore an issue for ongoing randomised scleroderma trials. Burt and colleagues addressed this problem by including
significant differences in vital organ outcome as stopping rules in the protocol (ie, much the same as deaths are routinely used).

Despite the small number of patients and short follow-up of ASSIST, the findings of this trial are important for patients with systemic sclerosis, the medical community, and policy makers. First, we should avoid the use of cyclophosphamide for severe forms of systemic sclerosis, when it “is unlikely to be clinically meaningfully effective”. Second, ASSIST reassures us about the safety of HSCT for systemic sclerosis when selection of patients, follow-up, and centre-effects are managed carefully. Third, ASSIST confirms the importance of non-myeloablative HSCT for severe systemic sclerosis to induce remission, while resetting the immune response. Fourth, the trial will stimulate interest in the area, before results of the two phase 3 trials (SCOT and ASTIS) are known, which differ from ASSIST in terms of their multicentre approach and in their control groups with longer duration and higher total doses of cyclophosphamide.

Results from the ongoing randomised trials for autologous HSCT in systemic sclerosis, although important, will not resolve all the questions. These challenges include optimal treatment intensity and risk of transplantation-related mortality; the role of CD34-selected grafts compared with unmanipulated grafts; choice of biological or genetic markers for subsets of patients most likely to benefit; assessments of outcome through new validated activity scores; definitions of drug-free remission; required durations of follow-up to assess risk of relapse; and definition of cure for an autoimmune disease such as systemic sclerosis for which the term cure is not defined. Although randomised trials are key, other types of studies are appropriate, and capture of data from all trials including non-randomised studies is important as promoted by the European Group for Blood and Marrow Transplantation (EBMT). Multicentre collaboration is crucial to establish the best therapeutic approach, with analysis of shared registry data and biological material obtained with adequate technical platforms. In this context, the European Orphan Disease Plan, which includes national and regional centres of reference and networks for HSCT in autoimmune diseases, might help to extend the important findings of ASSIST.

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