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Autologous Hematopoietic Stem Cell Therapy in Severe Systemic Sclerosis—Ready for Clinical Practice?

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Systemic sclerosis (SSc) is a life-threatening disease that includes a subset of patients with diffuse cutaneous systemic sclerosis (dcSSc; defined as widespread skin involvement) and internal organ involvement that has a mortality of 30–50% at 5 years (1). Conventional dose immunosuppressive therapy has limited efficacy in preventing disease progression and there are few data to support survival benefit (2). High-dose immunosuppression has been explored as an alternative to conventional dose immunosuppression. Despite the increased risk of toxicity, the rationale for high-dose immunosuppression is that SSc is an autoimmune disorder that progressively damages internal organs and is associated with chronic inflammation and systemic immunological abnormalities (3). Studies of high-dose immunosuppression (with autologous hematopoietic stem cell transplant [HSCT]) in SSc have demonstrated efficacy in preventing disease progression (1,4) and a single center trial demonstrated superiority of autologous HSCT over conventional therapy (Autologous non-myeloablative HSCT compared with pulse cyclophosphamide once per month for systemic sclerosis [ASSIST]) (4).

High dose immunosuppression is effective against other autoimmune diseases such as severe aplastic anemia and multiple sclerosis. Although the mechanisms underlying the benefit of autologous transplantation in autoimmune diseases are still not fully understood, increasing evidence supports the re-establishment of immunological tolerance (a series of immunological mechanisms that keep autoimmunity in check), in addition to a non-specific immunosuppressive effect. High-throughput T-cell receptor (TCR) β chain deep sequencing was analyzed following autologous HSCT for multiple sclerosis. In CD4⁺ T cells, dominant TCR clones (represented by unique TCR β DNA sequences) that were present prior to HSCT were undetectable following reconstitution, and patients developed a new, diverse TCR repertoire (5), suggesting immune tolerance.

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In this issue of JAMA, the European Group for Blood and Marrow Transplantation presents the first international, randomized controlled trial of autologous HSCT vs. pulse monthly cyclophosphamide (CYC) in 156 patients with early dcSSc (Autologous Stem Cell Transplantation International Scleroderma [ASTIS]) (6). For patients randomized to the HSCT arm, autologous CD34+ hematopoietic stem cells (HSC) were collected from CYC + cytokine (granulocyte-colony stimulating factor) mobilized peripheral blood, selected using antibody-conjugated magnetic beads and cryopreserved. A few weeks later, the conditioning regimen for HSCT consisted of high dose CYC and rabbit anti-thymocyte globulin (ATG), followed by re-infusion (autologous transplantation) of the patient's own thawed CD34+ cells. Patients in this trial, selected at 29 centers in Europe, had dcSSc and high risk of disease progression or already had internal organ involvement. The study showed significantly better long-term event-free survival and overall survival at a median follow up of approximately 6 years, and clinically meaningful improvements in objective and patient-reported outcome measures at 2 years. However, the trade-off was greater treatment-related mortality (10.1%) during the first year and greater grade 3 or 4 adverse events (62.9% vs. 37.0%) during the first two years of followup.

The majority of patients in this study had evidence of interstitial lung disease (ILD; > 85%), 10% had severe skin involvement with no lung, heart, and kidney involvement, and the remainder had cardiac involvement, renal involvement, or both. Cardio-pulmonary involvement (ILD and pulmonary arterial hypertension) is a leading cause of mortality in SSc (7) and current management of ILD includes oral or pulse CYC and MMF (mycophenolate mofetil) (2). Two placebo-controlled randomized trials of CYC in ILD demonstrated a modest effect on pulmonary physiology (8, 9) and lack of survival benefit in a decision analysis (10). Clinically meaningful improvement in percent FVC was seen after HSCT in the ASTIS and ASIST trials. High treatment-related mortality is consistent with other published reports (1) and no center effect was noted in the ASTIS trial, but an association was observed between current or past smoking and higher treatment-related mortality. Other key observations included clinically meaningful improvements in softening of skin (a surrogate for better survival), and in health status and preference-based measures. However, there was an increased incidence of viral infections and a significant decline in creatinine clearance in the HSCT group. In addition, overall mortality was higher in patients with pulmonary hypertension (defined as pulmonary arterial systolic pressure > 50 mmHg on echocardiogram or mean PAP > 25 mmHg on right heart catheterization, irrespective of treatment allocation).

The optimal conditioning regimen for autologous HSCT in SSc is not known. The regimen used in the ASTIS trial, CYC 200 mg/kg and ATG is a highly effective conditioning regimen used for decades in allogeneic HSCT for severe aplastic anemia. (11) This regimen is considered to be immunoablative, because it profoundly depletes lymphocytes, but it is not considered to be myeloablative, because endogenous hematopoiesis (neutrophils, platelets and erythrocytes) can reconstitute following a prolonged period of pancytopenia. The infusion of autologous CD34+ HSC helps to accelerate recovery of hematopoiesis and improves the safety of the high dose therapy. Other HSCT trials in SSc added total body irradiation to the conditioning regimen, but total body irradiation potentially increases the morbidity of the transplant (1). On the other hand, reducing the CYC dose in the

conditioning regimen might decrease the efficacy of the treatment and result in more disease relapse/ progression. Thus, the optimal dose intensity that provides the maximal benefit with minimum toxicity remains to be determined. This is particularly important in this patient population, for whom the treatment-related mortality associated with CYC (200 mg/kg) and ATG, probably reflects the effects of the preparative regimen on pre-existing cardiopulmonary injury caused by disease. The ASTIS trial included CD34+ cell selection, which served to further deplete the auto-reactive T cells from the peripheral blood stem cell graft. Future studies will need to determine whether CD34+ selection of the graft is beneficial or if depletion of T cells from the HSC graft leads to an increased risk of infection or treatment-related mortality.

ASTIS and other studies show that patient selection is critical in determining successful outcomes for HSCT (1,4,12). Cardio-pulmonary involvement is associated with high mortality in HSCT. Extensive invasive and non-invasive work up with cardiac MRI, transthoracic Doppler echocardiogram, and, right heart catheterization has been suggested before consideration for HSCT to evaluate for primary cardiac involvement, pericardial disease, and pulmonary hypertension (4, 12). Recommendations have been published for early detection and screening of pulmonary hypertension in SSc that facilitate right heart catheterization (13–15) and should be incorporated into therapeutic trial designs. Careful evaluation for primary cardiac disease and constrictive pericarditis with echocardiogram/ cardiac MRI should also be considered (12). Fluid challenge during right heart catheterization can also identify occult left heart disease (15). There is a limited window of therapeutic opportunity in which a patient with progressive SSc and internal organ involvement can be evaluated for HSCT (2). In practice, the natural history of rapid disease progression makes some patients ineligible for HSCT due to progressive and advanced internal organ involvement (2). In addition, delayed or non-approval of HSCT by medical insurance carriers was a barrier encountered in an ongoing multicenter NIH-funded clinical trial (stem cell transplant vs. cyclophosphamide [SCOT; NCT00114530]). Further cost-effectiveness analysis of ASTIS data will support and facilitate this approval process.

Although it would be optimistic to consider that HSCT could be ‘curative’ for SSc, disease relapse occurred in up to 37% of patients at later time points after HSCT (1, 16). In the ASTIS trial, disease relapsed in 22.4% of patients assigned to HSCT at 12–24 months as defined by the need for immunosuppressive therapy. To address the issue of post-transplant disease relapse, the STAT trial [current US multicenter HSCT trial for SSc, referred to as the STAT trial (Scleroderma Treatment with Autologous Transplant; NCT 01413100), sponsored by the Scleroderma Research Foundation] has added 2 years of post-HSCT MMF maintenance therapy. Since it is known that MMF can be safely given to modulate the immune system after allogeneic HSCT, the hypothesis to be tested is whether MMF maintenance therapy can prevent or delay the recurrence of SSc after autologous HSCT.

Is HSCT ready for clinical practice? Studies completed so far have all shown survival benefit of HSCT and higher morbidity compared to standard of care treatments. Patients who are candidates for HSCT should be enrolled in protocols that aim to identify translational markers for disease, improve the treatment regimen and provide careful follow-up to evaluate long term outcome. In addition, highly specialized centers that provide both

scleroderma care and HSCT care are important for successful outcome as SSc is an uncommon disease and patients may have fragile organ function that requires careful monitoring and experienced intervention. The treatment-related mortality in SSc in ASTIS is higher when compared to other autoimmune diseases. In this context, the results from SCOT study being conducted in specialized transplant/scleroderma centers in US are eagerly awaited. Treatment-related mortality will be a key determinant as to whether HSCT will be offered by physicians and accepted by patients. However, data from SCOT will not be available until 2017.

In the meantime, recommendations are needed about which patients should be offered HSCT and whether HSCT should be offered as an upfront treatment (especially in patients with dcSSc with internal organ involvement) or as a salvage procedure. Currently consideration should be limited to patients with: dcSSc within the first 4–5 years of onset with mild-to-moderate internal organ involvement (severe internal organ involvement will make patients ineligible due to risks associated with HSCT), or limited cutaneous SSc with progressive internal organ involvement, and should be generally restricted to patients who have failed to improve or have worsened on conventional immunosuppressive agents and who are not active smokers. Finally, 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 SSc.

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