Stem Cell Transplantation for Systemic Sclerosis in Israel: A New Star Is Rising

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Systemic sclerosis (SSc) is an immune-mediated rare autoimmune disease with a prevalence of 50–300 per million people. SSc is characterized by vascular alterations and progressive fibrosis of the skin and internal organs [1]. Disease progression is heterogeneous, with skin and organ involvement varying across patients. In patients with rapidly progressive diffuse cutaneous SSc (dcSSc), 5-year and 10-year [2] mortality rates can be as high as 30% and 50%, respectively, depending on the extent of heart, lung, and kidney involvement [3].

For patients with severe and rapidly progressing disease, autologous hematopoietic stem cell transplant (aHSCT) is the only treatment so far that has shown efficacy in terms of survival and progression free survival. The therapeutic mechanism of action of aHSCT in SSc involves intense initial immunosuppression during a preconditioning regimen that will eradicate the patient's autoimmune-activated cells [2,4], followed by infusion of autologous hematopoietic stem cells (HSCs) to help repopulate the hematopoietic system and reset the immune response, which occurs partly through thymic reprocessing or increased regulatory T-cell activity. Since the first European Society for Blood and Marrow Transplantation (EBMT) treatment consensus in 1997, the use of aHSCT has progressively increased with more than 4000 patients treated by aHSCT worldwide for autoimmune diseases. As of July 2019, 3000 patients had been treated with aHSCT for an autoimmune disease in the EBMT registry alone. Among these, 600 were patients treated for SSc, making systemic sclerosis the second most frequently aHSCT-treated autoimmune disease after multiple sclerosis [5]. In this issue of the *Israel Medical Association Journal* (*IMAJ*), Rimar and colleagues [6] reported on the outcomes of the first five patients to be treated with aHSCT for severe progressive SSc in Israel. Israel is the newest nation to join the EBMT Autoimmune Disease Working Party network of participating transplant centers. Rimar and colleagues reported very promising results, which reflect the major strides that have been made toward improving treatment safety in recent years, largely as a result of a global collaborative effort.

Support for aHSCT in severe dcSSc was first provided by results from early phase I-II trials [7,8], showing rapid improvements in skin scores [9], functional status [10], and stabilization of lung function. Major regression of fibrosis was also confirmed in these patients by skin histology [9] and regression of lung fibrosis on computed tomography (CT) scan [11], which had never been previously observed with any other treatment of SSc. Long-term published follow-up confirmed that these outcomes were sustained for more than 5 to 7 years [8]. In France the longest post-transplant remission after aHSCT for SSc is currently 20 years (personal data). While transplant-related mortality rates were high in the early phase I-II studies, these were nevertheless strikingly lower than the estimated 5-year mortality rate due to disease progression reported in these patients (30%) [3]. Three subsequent randomized clinical trials (ASSIST in 2011 [11], ASTIS in 2014 [12], SCOT in 2018 [13]) successively demonstrated that aHSCT allows better overall and event-free survival as compared to the treatment standard intravenous cyclophosphamide for early rapidly progressive SSc with significant gains at 1, 2, and up to 7 years after aHSCT.

The ASTIS trial [12] compared aHSCT (cyclophosphamide, antithymocyte globulin [ATG], and CD34+ cells selected graft) versus a monthly intravenous pulse of cyclophosphamide 750 mg/m for 12 months. ASTIS was an international, multicenter, investigator-based, open-label, phase III trial. It was a ground-breaking academic collaborative project coordinated by the EBMT in collaboration with the European League Against Rheumatism (EULAR). These two leading entities in the field supported this pivotal and unique study. From 2001 to 2009, 156 patients from 10 countries with early dcSSc were recruited and followed until the end of October 2013. The primary endpoint was event-free survival, defined as time from randomization until the occurrence of death or persistent major organ failure. Even though aHSCT therapy showed more treatment-related mortality in early follow-up (1 year), long-term, event-free, and overall survival rates were higher in the aHSCT treatment group relative to the control cyclophosphamide group.

Other studies, such as the single-center ASSIST study conducted in Chicago, USA [11], also elegantly showed that both skin and lung fibrosis regressed significantly after aHCST. Both the ASSIST and ASTIS trials used a non-myeloablative regimen of cyclophosphamide and rabbit anti-thymocyte globulin. The trials differed in the concentration of cyclophosphamide used in the conditioning phase (4 g/m^2 [ASTIS] and 2 g/m^2 [ASSIST]) and in the fact that the ASTIS trial enriched for CD34+ cells ex vivo prior to infusion, while ASSIST did not. In the ASTIS trial, transplant-related mortality was 10% at a median follow-up of 5.8 years. In the ASSIST trial, the rate of transplant-related mortality was 0% at the 2-year follow-up [11], and 6% at 5 years in the cohort of patients further treated with the ASSIST like regimen [14]. Treatment-related mortality was found to be mainly attributable to SSc-related cardiac dysfunction.

The SCOT trial [13], which used a low dose of cyclophosphamide, showed lower rates of cardiac-related toxicity than ASSIST [11] and ASTIS [12]. However, the rate of major (grade 4) adverse events, such as development of malignancies, was higher in the SCOT trial [13] compared to ASTIS [12] (85% vs. 37%). This result was associated with the total body irradiation-based myeloablative regimen used in the study. Thus, these studies revealed that intensive cyclophosphamide regimens pose a mortality risk in patients with cardiac dysfunction, and total-body irradiation increases the risk of cancer. The myeloablative regimen used in the SCOT trial [13] also failed to improve lung function, as opposed to the ASSIST [11] and ASTIS [12] trials, which both reported that FVC and total lung capacity were improved [15]. Together, these trials led to the understanding that treatment safety with non-myeloablative aHSCT could be increased by conducting more extensive cardiac screening, including echocardiogram, right heart catheterization, and MRI [16].

Subsequent studies identified other individual risk factors for complications following aHSCT, which helped to build an ideal patient profile to guide patient screening and selection. Patients with rapidly progressive skin involvement and only mild/moderate lung involvement who were within 4 to 5 years of diagnosis were identified as most likely to benefit from aHSCT, while patients with severe organ involvement, current smokers, or patients with a history of smoking were identified as high risk for treatment-related mortality [16,17]. The degree of center experience and expertise was also a crucial factor in predicting outcomes patients with an autoimmune disease undergoing a first aHSCT [8,17]. These findings led to revision and update of the EBMT and EULAR guidelines, which recommended that patients be referred to a center with Joint Accreditation Committee ISCT-Europe and EBMT (JACIE) accreditation or equivalent, with appropriate inter-disciplinary interaction can optimize patient selection and management [5]. aHSCT is indicated in SSc patients presenting with severe or rapidly progressive disease and **(a)** disease duration less than 5 years since onset of first non-Raynaud's symptoms and a modified Rodnan skin score (mRSS) > 15 plus lung involvement with a diffusing capacity of carbon-monoxide (DLCO) and/or forced-vital-capacity (FVC) ≤ 70% of predicted and evidence of interstitial lung disease on high resolution CT scan, cardiac involvement with conduction or rhythm disturbance, pericarditis, or renal involvement with proteinuria > 0.3 grams/24 hours or **(b)** disease duration of 2 years or less and no major organ dysfunction as defined above provided they had an mRSS of at least 20 and an acute phase response. Comprehensive cardiopulmonary screening and pre-transplant evaluation of heart, lung, kidney and gastrointestinal function is critically important to exclude patients at high risk of treatment-related mortality.

In their study, Rimar and colleagues [6] rigorously applied our current knowledge and understanding of best practices, in accordance with updated clinical practice guideline recommendations [16-18]. The treatment protocol used a non-myeloablative conditioning regimen of 200 mg/kg of cyclophosphamide and 7.5 mg/kg of ATG, without CD34+ selection. SSc patients included in the study were younger than 65 years of age, had rapidly progressive disease diagnosed within 5 years, a mRSS score > 15, and lung fibrosis with deteriorating lung function (FVC or DLCO ≤ 70% predicted) despite standard therapy. Patients underwent a thorough screening process, which included a clinical exam, chest and abdomen CT scan, pulmonary function tests, laboratory tests, endoscopy in the presence of anemia, and a complete cardiac workup according to good clinical practices guidelines.

This study by Rimar [6] and colleagues provides valuable insights into the impact of applying our updated knowledge of the factors affecting safety and efficacy outcomes with aHSCT in patients with rapidly progressive SSc. In these first five cases with follow-ups of up to 3.5 years, severe adverse events were reported including, cyclophosphamide-related congestive heart failure, ATG-related capillary leak syndrome, and SSc renal crisis, but these conditions resolved and there have been no treatment-related deaths in these five severly affected SSc patients. One relapse was noted 1 year after transplant. The outcomes beyond 5 years will be eagerly awaited by aHSCT community.

As pointed out by Rimar and colleagues [6], this knowledge and experience has raised new questions and identified new concerns, which will continue to be addressed collaboratively by the EBMT network in the coming years. For example, there are ongoing questions about whether the time since diagnosis to qualify for aHSCT should be revised, how to improve mobilization protocols, and whether CD 34+ selection provides a treatment benefit [19]. Post-transplant care will also be a very important area to more clearly define in the future. There are questions about when to re-initiate immunosuppressive therapy, whether it should be given routinely, or only in case of relapse. New agents coming on the scene such as antifibrotics are also going to influence this therapeutic area, and aHSCT trials will likely have to

compare to cyclophosphamide combination therapies.

OUTCOMES

The Rimar study [6] contributes to a growing body of evidence that use of aHSCT in patients with severe and rapidly progressive SSc can result in significant improvements in patient quality of life [10] and survival [8-15], and provides new data on outcomes following best practice recommendations from updated clinical practice guidelines. Worldwide collaboration using shared protocols and common data will allow to improve patient care and design future international trials to achieve more effective and safer aHSCT procedures [5,15,16], after careful pre-transplant evaluation in accredited expert centers, where both disease experts and hematologists have agreed to work in tandem.

Data reporting and biobanking are central to the development of aHSCT for AD and unique MED-A and specific MED-B forms of SSc disease can be downloaded at http://www.ebmt.org. Over time, knowledge on clinical management and on immunological mechanisms associated with aHSCT for AD has evolved into a very pronounced learning curve, with significant improvements in transplant-related safety and in disease-free survival. In fact, there is a noticeable center effect among the hundreds of aHCST already reported, in which centers more experienced, with larger patient series, report better outcome [5,20]. This finding underscores the importance of having educational events and of creating a network of teaching professionals with both experts in SSc and in aHSCT to expand AD transplant activity, yet preserving quality of health care.

CONCLUSIONS

The success of the French and Israel collaboration is based on mutual friendship and respect to good clinical practice guidelines, the capacity to share regularly updated knowledge using new technologies for information, as we constructed within the French Reference Center MATHEC Network (www.mathec.com) from common coordinated efforts, where over the past 5 years, collaboration between rheumatologists and hematologists contributed to the development of autologous Hematopoiesis stem cell transplantation for severe systemic sclerosis patients.

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References

1. Van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737-47.
2. Farge D, Henegar C, Carmagnat M, et al. Analysis of immune reconstitution after autologous bone marrow transplantation in systemic sclerosis. *Arthritis Rheum* 2005; 52: 1555-63.
3. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1897-905.
4. Farge D, Arruda LC, Brigant F, et al. Long-term immune reconstitution and T cell repertoire analysis after autologous hematopoietic stem cell transplantation in systemic sclerosis patients. *J Hematol Oncol* 2017; 10: 21.
5. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv* 2017; 1: 2742-55.
6. Rimar D, Butbul Avriel Y, Gefen A, et al. Autologous hematological stem cell transplantation for systemic sclerosis in Israel. *IMAJ* 2020; 22: 104-10.
7. Farge D, Marolleau JP, Zohar S, et al. Autologous bone marrow transplantation in the treatment of refractory systemic sclerosis: early results from a French multicentre phase I-II study. *Br J Haematol* 2002; 119: 726-39.
8. Farge D, Labopin M, Tyndall A, et al. Autologous hematopoietic stem cell transplantation for autoimmune diseases: an observational study on 12 years' experience from the European Group for Blood and Marrow Transplantation Working Party on Autoimmune Diseases. *Haematologica* 2010; 95: 284-92.
9. Verrecchia F, Laboureau J, Verola O, et al. Skin involvement in scleroderma--where histological and clinical scores meet. *Rheumatology (Oxford)* 2007; 46: 833-41.
10. Puyade M, Maltez N, Lansiaux P, et al. Health-related quality of life in systemic sclerosis before and after autologous hematopoietic stem cell transplant-a systematic review. *Rheumatology (Oxford)* 2019; pii: kez300.
11. Burt RK, Shah SJ, Dill K, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet* 2011; 378: 498-506.
12. Van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs. intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA* 2014; 311: 2490-8.
13. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med* 2018; 378: 35-47.
14. Burt RK, Oliveira MC, Shah SJ, et al. Cardiac involvement and treatment-related mortality after non-myeloablative haemopoietic stem-cell transplantation with unselected autologous peripheral blood for patients with systemic sclerosis: a retrospective analysis. *Lancet* 2013; 381: 1116-24.
15. Burt RK, Farge D. Systemic sclerosis: Autologous HSCT is efficacious, but can we make it safer? *Nat Rev Rheumatol* 2018; 14: 189-91.
16. Farge D, Burt RK, Oliveira MC, et al. Cardiopulmonary assessment of patients with systemic sclerosis for hematopoietic stem cell transplantation: recommendations from the European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Party and collaborating partners. *Bone Marrow Transplant* 2017; 52: 1495-503.
17. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012; 47: 770-90.
18. Alexander T, Bondanza A, Muraro PA, et al. SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking. *Bone Marrow Transplant* 2015; 50: 173-80.
19. Oliveira MC, Labopin M, Henes J, et al. Does ex vivo CD34+ positive selection influence outcome after autologous hematopoietic stem cell transplantation in systemic sclerosis patients? *Bone Marrow Transplant* 2016; 51: 889.
20. Snowden JA, Badoglio M, Labopin, et al. European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP); EBMT Paediatric Working Party (PWP); Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT); EBMT (JACIE). Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv* 2017; 1 (27): 2742-55.

"I feel fairly certain that my hatred harms me more than the people whom I hate"

Max Frisch (1911–1991), architect, playwright, and novelist