

DOI: 10.46765/2675-374X.2023V4N1P182

CONSENSUS UPDATE

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES

Milton Artur Ruiz¹, Maria Carolina Oliveira^{2,3}, Daniela Moraes², Juliana Elias Dias², Lilian Piron-Ruiz¹, Andreza Feitosa Ribeiro⁴, Morgani Rodrigues⁴, Nelson Hamerschlak⁴

1 Bone Marrow Transplantation and Cell Therapy Unit, Associação Portuguesa de Beneficência de São José do Rio Preto, São José do Rio Preto, Brazil; *2* Department of Internal Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; *3* Center for Cell-based Therapy, Regional Blood Center, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil; *4* Bone Marrow Transplantation Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil

Corresponding author: Maria Carolina Oliveira (mcarolor@usp.br)

Received: 11 Nov 2022 • Revised: 30 Nov 2022 • Accepted: 13 Jan 2023.

ABSTRACT

Autoimmune diseases are an important field for the development of hematopoietic stem cell transplantation (HSCT). The Brazilian Society for Cellular Therapy and Bone Marrow Transplantation (Sociedade Brasileira de Terapia Celular e Transplante de Medula Óssea, SBTMO) organized consensus meetings for the Autoimmune Diseases Group, to review the available literature on HSCT for autoimmune diseases, aiming to gather data that support the procedure for these patients. Three autoimmune diseases for which there are evidence-based indications for HSCT are multiple sclerosis, systemic sclerosis and Crohn's disease. The professional stem cell transplant societies in North America (ASTCT), Europe (EBMT) and Brazil (SBTMO) currently consider HSCT as a therapeutic modality for these three autoimmune diseases. The data are here updated.

Keywords: Autoimmune diseases. Hematopoietic stem cell transplantation. Multiple sclerosis. Systemic sclerosis. Crohn's disease.

Autologous hematopoietic stem cell transplantation (AHSCT) has been used worldwide as treatment for autoimmune disease patients¹. The procedure aims to promote immune depletion, eliminate autoreactive lymphocytes and reprogram the immune system, restoring long-lasting immune tolerance. As result, patients maintain long-term clinical remission in absence of further immunosuppression. The three most important and current indications for AHSCT are multiple sclerosis, systemic sclerosis and Crohn's disease (Table 1)¹.

TABLE 1 - Randomized clinical studies on AH SCT for autoimmune diseases

STUDY	MAIN CONTRIBUTION TO THE FIELD
Multiple Sclerosis	
ASTIMS trial ² <i>Italy and Spain (EBMT), intermediate-intensity regimen, 21 patients</i>	Transplanted patients improved in disability and had fewer relapses than conventionally-treated patients over a 5-year follow-up. All patients had highly inflammatory and active MS.
MIST trial ³ <i>Multicenter, non-myeloablative regimen, 110 patients</i>	Transplanted patients did not present new T2 lesions on MRI compared to those treated with mitoxantrone. No effect on disability, but most patients were in secondary-progressive phase.
Systemic Sclerosis	
ASSIST trial ⁴ <i>Single USA center, non- myeloablative regimen, 19 patients</i>	Autologous transplant was more effective than monthly intravenous cyclophosphamide in controlling skin thickening, lung function and quality of life, over a 24-month follow-up.
ASTIS trial ⁵ <i>European multicenter, non- myeloablative regimen, 156 patients</i>	Transplanted patients had higher overall survival, progression-free survival and quality of life than conventionally-treated patients over a 5-year follow-up.
SCOT trial ⁶ <i>USA multicenter, myeloablative regimen, 75 patients</i>	Transplanted patients had higher overall survival and progression-free survival than conventionally-treated patients over a 5-year follow-up.
Crohn's Disease	
ASTIC trial ^{7,8} <i>European multicenter, non- myeloablative regimen, 45 patients</i>	No differences in sustained remission composite scores (clinical, radiological and endoscopic) between transplanted and only mobilized patients. Secondary outcomes of disease activity, endoscopic activity and use of medical therapy favored transplanted patients.

AH SCT: autologous stem cell transplantation; MRI: magnetic resonance imaging.

The American Society for Cellular Transplantation and Therapy (ASTCT)^{9,10}, the European Society for Blood and Marrow Transplantation (EBMT)^{11,12}, the European League Against Rheumatism (EULAR)¹³ and the Brazilian Society of Bone Marrow Transplantation (SBTMO)^{14,15} currently consider AH SCT as part of the already established therapeutic strategies for these autoimmune disorders, apart from the research setting.

Since the last consensus meeting published in 2021¹⁵, a few new studies have been added to the field, however not changing the recommendations. Novel studies include a regimen of lower intensity, with decreased dosage of cyclophosphamide for systemic sclerosis patients¹⁶. Although this trial shows less cardiac toxicity and shortened duration of neutropenia, it still has to be investigated by other centers and long-term outcomes should be compared to conventional treatment in a randomized controlled setting. A prospective multicenter study from

the EBMT and partners also confirmed successful clinical outcomes of systemic sclerosis patients over a 24-month follow-up after AH SCT¹⁷. In multiple sclerosis, AH SCT was used as first line therapy in patients with aggressive disease, with successful clinical and radiological outcomes over median follow-up of 30 months¹⁸. Also, a Mexican group has reported their experience with one thousand transplanted patients using a split-cyclophosphamide dose strategy¹⁹. The authors claim that by splitting the total dose, the transplant regimen becomes safer to the heart. This approach, however, should be tested in other autoimmune disease settings, since cardiotoxicity is not a key problem in multiple sclerosis transplants as it is in other diseases such as systemic sclerosis^{20,21}. In addition, reports on the long-term outcomes of these patients are pending. Very recently, the group from Chicago (USA) reported their “real-world” experience with more than 500 patients transplanted for multiple sclerosis²². The authors show positive outcomes for patients with the relapsing-remitting form of the

disease, who improve disability and sustain remission over time. On September 2nd, 2021, the Brazilian Federal Council of Medicine issued a favorable opinion on AH SCT as treatment for multiple sclerosis.

Allogeneic transplants for autoimmune diseases remain limited to the research setting, in view of the excessive toxicity and need to improve clinical protocols¹¹.

In conclusion, data from national and international studies provide scientific support to recommend AH SCT as treatment for multiple sclerosis, systemic sclerosis and Crohn’s disease (Table 2). Allogeneic transplantation, however, should still be further evaluated in the experimental setting.

TABLE 2 – SBTMO recommendations for AH SCT in autoimmune diseases

Disease	Autologous transplantation	Allogeneic transplantation		
		MSD	MUD	MMAD
Multiple sclerosis	Recommended/I	Experimental/III	Not recommended/III	Not recommended/III
Systemic sclerosis	Recommended/I	Experimental/III	Not recommended/III	Not recommended/III
Crohn’s disease	Recommended/II	Experimental/III	Not recommended/III	Not recommended/III

SBTMO: Brazilian Society of Bone and Marrow Transplantation; AH SCT: autologous hematopoietic stem cell transplantation. MSD: matched sibling donor; MUD: matched unrelated donor; MMAD: mismatched alternative donor. Table created by the authors. Recommendations are categorized according to described in reference 11.

REFERENCES

1. Snowden JA, Sharrack B, Akil M, et al. Autologous haematopoietic stem cell transplantation (aHSCT) for severe resistant autoimmune and inflammatory diseases - a guide for the generalist. *Clin Med (Lond)*. 2018;18(4):329-34.
2. Mancardi GL, Sormani MP, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. *Neurology*. 2015;84(10):981-8.
3. Burt RK, Balabanov R, Burman J, et al. Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis: A Randomized Clinical Trial. *JAMA*. 2019;321(2):165-74.
4. Burt RK, Shah SJ, Dill K, et al. Autologous nonmyeloablative 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(9790):498-506.
5. 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(24):2490-8.
6. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, et al. Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma. *N Engl J Med*. 2018;378(1):35-47.
7. Hawkey CJ, Allez M, Clark MM, et al. Autologous Hematopoietic Stem Cell Transplantation for Refractory Crohn Disease: A Randomized Clinical Trial. *JAMA*. 2015;314(23):2524-34.
8. Lindsay JO, Allez M, Clark M, et al. Autologous stem-cell transplantation in treatment-refractory Crohn’s disease: an analysis of pooled data from the ASTIC trial. *Lancet Gastroenterol Hepatol*. 2017;2(6):399-406.

9. Cohen JA, Baldassari LE, Atkins HL, et al. Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2019;25(5):845-54.
10. Sullivan KM, Majhail NS, Bredeson C, et al. Systemic Sclerosis as an Indication for Autologous Hematopoietic Cell Transplantation: Position Statement from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2018;24(10):1961-4.
11. Duarte RF, Labopin M, Bader P, et al; European Society for Blood and Marrow Transplantation (EBMT). Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant.* 2019;54(10):1525-52.
12. Sharrack B, Saccardi R, Alexander T, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant.* 2020;55(2):283-306.
13. Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis.* 2017;76(8):1327-39.
14. Oliveira MC, Elias JB, Moraes DA, et al. A review of hematopoietic stem cell transplantation for autoimmune diseases: multiple sclerosis, systemic sclerosis and Crohn's disease. Position paper of the Brazilian Society of Bone Marrow Transplantation. *Hematol Transfus Cell Ther.* 2021;43:65-86.
15. Oliveira MC, Ruiz MA, Moraes D, et al. HSCT for autoimmune diseases. *JBMTCT.* 2021;2(1):127-30.
16. Burt RK, Han X, Quigley K, et al. Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: a pilot safety study that decreases neutropenic interval to 5 days. *Bone Marrow Transplant.* 2021;56:50-59.
17. Henes J, Oliveira MC, Labopin M, et al. Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party. *Haematologica.* 2021;106:375-83.
18. Das J, Snowden JA, Burman J, et al. Autologous haematopoietic stem cell transplantation as a first-line disease-modifying therapy in patients with 'aggressive' multiple sclerosis. *Mult Scler.* 2021;27(8):1198-1204.
19. Olivares-Gazca JC, Guerrero-Pesqueira F, Murieta-Alvarez I, et al. J. Splitting the Total Dose of Cyclophosphamide in Two Blocks Apart during the Conditioning of Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis Results in Diminished Cardiotoxicity: Experience in 1,000 Patients. *Rev Invest Clin.* 2022;74:1-3.
20. 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(9872):1116-24.
21. 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(11):1495-503.
22. Burt RK, Han X, Quigley K, et al. Real-world application of autologous hematopoietic stem cell transplantation in 507 patients with multiple sclerosis. *J Neurol.* 2022;269(5):2513-26.