Autologous hematopoietic stem cell transplantation for relapsing-remitting multiple sclerosis: A single-center institutional care protocol

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ABSTRACT

Relapsing-remitting multiple sclerosis (RRMS) may remain clinically and radiologically active despite sequential exposure to high-efficacy disease-modifying therapies. In carefully selected patients with highly active inflammatory RRMS, autologous hematopoietic stem cell transplantation (AHSCT) has demonstrated superior inflammatory control and durable rates of no evidence of disease activity, with low treatment-related mortality rates in experienced centers. AHSCT promotes immune renewal through high-dose immunoablation followed by autologous stem cell rescue, aiming to restore immune tolerance. Here, we describe a structured institutional standard-of-care protocol for AHSCT in RRMS, developed to support safe referrals and harmonize neurology-hematology collaboration within a Brazilian tertiary center. By consolidating a transparent and safety-focused care pathway aligned with national and international guidance, this manuscript aims to facilitate standardized patient selection, optimize risk mitigation, and strengthen multidisciplinary communication between referring neurologists and transplant teams.

Keywords: Multiple sclerosis; Stem cell transplantation; Clinical protocol.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease and a leading cause of non-traumatic neurological disability in young adults worldwide.[1] Despite substantial advances in high-efficacy disease-modifying therapies (HE-DMTs), a subset of patients continues to experience disease activity.[2] These individuals may exhibit highly active inflammatory relapsing-remitting MS (RRMS), characterized by recurrent clinical relapses, new or enlarging *magnetic resonance imaging* (MRI) lesions, and early disability accumulation despite optimized treatment strategies.[2,3]

Autologous hematopoietic stem cell transplantation (AHSCT) addresses this therapeutic gap through intensive immunoablation followed by autologous stem cell rescue, enabling immune repertoire renewal and re-establishment of tolerance rather than sustained mechanism-specific immune targeting.[4-6] In randomized trials and large observational cohorts, AHSCT has demonstrated superior control of clinical and radiological disease activity compared with continued pharmacologic escalation in carefully selected RRMS populations, with durable rates of no evidence of disease activity (NEDA).[7,8] Contemporary data from experienced centers report treatment-related mortality rates below 0.3%, reflecting advances in patient selection, supportive care, and intermediate-intensity conditioning regimens.[9,10]

Despite substantial advances in transplant safety, access to AHSCT remains heterogeneous worldwide, and structured descriptions of integrated neurology-to-transplant clinical pathways are limited in several healthcare systems.[11] Although AHSCT entails significant upfront costs, health-system analyses suggest that it may become cost-effective over mid-term horizons compared with prolonged high-cost pharmacotherapy in selected patients with highly active inflammatory RRMS.[12] In Brazil, national transplant societies endorse hematopoietic stem cell transplantation for autoimmune diseases, including MS, when performed in experienced centers within structured multidisciplinary programs.[13-15]

Accordingly, we present a single-center institutional standard-of-care protocol to standardize referrals, patient selection, risk mitigation, and longitudinal follow-up, aligned with contemporary international and national recommendations.

METHODS

Study design and setting

This manuscript describes a single-center institutional standard-of-care protocol for AHSCT in adults with highly active inflammatory RRMS who continue to exhibit clinical and/or radiological disease activity despite HE-DMTs. It is structured as a clinical care pathway rather than a clinical trial, to standardize patient selection, transplant delivery, and safety monitoring in routine practice.[3,15]

The protocol includes predefined early post-transplant assessments of clinical, radiological, and functional outcomes, followed by continued long-term neurological surveillance. Multidisciplinary decision-making is required and involves neurology, hematology/bone marrow transplantation, infectious diseases, cardiology, and rehabilitation.

Standardized inpatient and outpatient procedures include eligibility confirmation, pre-transplant workup, supportive care, infection prophylaxis, viral reactivation surveillance, and structured neurological follow-up with MRI and validated disability and functional measures, including the Expanded Disability Status Scale (EDSS) and objective performance testing when feasible.

Inclusion and exclusion criteria for AHSCT in RRMS

Patient eligibility was established in accordance with contemporary international consensus recommendations and national transplant guidance, prioritizing individuals with highly active inflammatory RRMS while minimizing procedural risk. The complete set of inclusion and exclusion criteria is presented in Fig. 1.

Pre-transplant evaluation and inpatient preparation

After multidisciplinary confirmation of eligibility, patients are admitted to the dedicated oncology-hematology inpatient unit. Drug washout is guided by the pharmacokinetic and immunological profile of prior disease-modifying therapies.[3,16]

Baseline evaluation includes a comprehensive neurological examination, EDSS scoring, and brain and spinal MRI with gadolinium within 30 days before conditioning.[3,16] Additional assessments include hematology consultation, cardiopulmonary evaluation, renal and hepatic function tests, infectious disease screening, nutritional assessment, psychological evaluation, and fertility counseling.[11]

Upon admission, supportive measures are initiated according to institutional protocol. Antiparasitic prophylaxis reflects regional epidemiology and includes albendazole 400 mg once daily for 3 days plus ivermectin 200 µg/kg (typically 6-18 mg) as a single dose, given the risk of hyperinfection during profound immunosuppression.[17,18] Gastric protection with pantoprazole 40 mg daily is routinely prescribed.

Inclusion Criteria	Exclusion Criteria
• RRMS according to revised 2017/2024 McDonald criteria	• Recent cytotoxic drug exposure
• Failure of prior high-efficacy DMTs	• Major organ dysfunction or high procedural risk
• Age 18-45 years	• Active infection
• Disease duration ≤ 10 years	• Inability to provide informed consent
• EDSS ≤ 6.0	• Prior cellular therapy or radiation
• Clinical activity within 12 months despite high-efficacy DMT	• Active peptic ulcer disease
• MRI inflammatory activity within 12 months	• Relapse within 1 month prior to evaluation
• Signed informed consent	• Myelodysplasia or non-autoimmune cytopennia
	• Limited life expectancy
	• Immunosuppressive therapy <3 months or corticosteroids < 30 days
	• PPMS or SPMS without inflammatory activity
	• Hypersensitivity to rabbit/rat/E. coli-derived proteins
	• Uncontrolled psychiatric disorder or substance abuse
	• Karnofsky < 70% or ECOG > 2
	• LVEF < 50%
	• DLCO < 50%

DLCO: diffusion capacity of the lung for carbon monoxide; ECOG: Eastern Cooperative Oncology Group performance status; LVEF: left ventricular ejection fraction; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis. Source: Elaborated by the authors.

Figure 1. Eligibility criteria for AHSCT in RRMS. Eligibility was defined according to contemporary international consensus recommendations and national transplant guidance.

Stem cell mobilization and collection

Peripheral blood stem cell mobilization is performed using cyclophosphamide 2 g/m^2 intravenously as a single dose, followed by granulocyte colony-stimulating factor (G-CSF) 10 µg/kg/day starting on day +5 and continued until completion of leukapheresis. [3,9,16] The combination of cyclophosphamide and G-CSF is preferred in highly active inflammatory RRMS to enhance mobilization yield while reducing the theoretical risk of G-CSF-associated disease reactivation observed with G-CSF alone in autoimmune conditions.[4,9] Short-course corticosteroid prophylaxis may be considered at the discretion of the transplant and neurology teams.

Peripheral blood stem cells are collected by leukapheresis and cryopreserved. In accordance with EBMT recommendations for non-malignant indications, the target CD34+ dose is ≥ 5 × 10^6 cells/kg, with a minimum acceptable threshold of 2 × 10^6 cells/kg.[11] Plerixafor is reserved for poor mobilizers according to institutional criteria.

Central venous catheter placement is preferably performed early during hospitalization to minimize bleeding risk associated with potential thrombocytopenia during mobilization.

Conditioning regimen

The cyclophosphamide plus rabbit anti-thymocyte globulin (CY/ATG) regimen was selected in accordance with contemporary international consensus recommendations and cumulative clinical experience in MS. Current EBMT guidance and expert statements recognize CY/ATG as the most widely used non-myeloablative, intermediate-intensity conditioning strategy in RRMS, balancing effective immune ablation with an acceptable safety profile.[4,9] Randomized and large observational cohorts employing cumulative cyclophosphamide doses of 200 mg/kg combined with rabbit ATG (5-7.5 mg/kg total) have demonstrated durable inflammatory suppression with low contemporary treatment-related mortality.[6,18]

The CY/ATG dosing schedule follows commonly used non-myeloablative, intermediate-intensity regimens reported in international consensus guidance and large clinical series.[4,9,11] Cyclophosphamide is administered at 50 mg/kg/day intravenously for 4 consecutive days (total cumulative dose 200 mg/kg). Mesna uroprotection is provided at 1.4 times the total cyclophosphamide dose, administered as 15 mg/kg immediately before cyclophosphamide and 15 mg/kg at 3, 6, 9, and 12 hours after each cyclophosphamide infusion.

Rabbit ATG (thymoglobulin) is administered over 5 consecutive days prior to stem cell infusion (day 0) using an escalating schedule: 0.5 mg/kg/day on day -5, 1.0 mg/kg/day on day -4, and 1.5 mg/kg/day on days -3 to -1 (total cumulative dose 6.0 mg/kg). The first ATG infusion is delivered over 12 hours under close monitoring. Methylprednisolone 2 mg/kg intravenously is initiated 1 day before ATG and administered 15 minutes prior to each ATG dose; corticosteroids are continued for 24-48 hours after the final infusion, or longer if clinically indicated, to mitigate infusion-related reactions, in addition to standard antihistamine and antipyretic premedication.

Stem cell reinfusion and early post-transplant care

Autologous stem cells are reinfused on day 0. Engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count $\geq 0.5 \times 10^9$/L, in accordance with established hematopoietic stem cell transplantation criteria.[19] Standard antimicrobial prophylaxis and viral reactivation monitoring, including cytomegalovirus surveillance through day +100, are performed according to international transplant infectious disease guidelines.[19]

Follow-up

Neurological follow-up is jointly coordinated by the MS and transplant teams and includes structured clinical and radiological assessments at 6, 12, 18, 24, and 36 months after transplantation, or earlier if clinically indicated.[3] Brain MRI with gadolinium is performed according to this schedule to evaluate inflammatory activity and structural evolution.

Disability is assessed using the EDSS complemented by objective functional measures, including the Timed 25-Foot Walk, 9-Hole Peg Test, and the Symbol Digit Modalities Test providing multidimensional evaluation of physical and cognitive domains.[6]

Clinical relapses, MRI activity, and disability trajectory are systematically documented to assess sustained inflammatory remission and long-term disease stability. Transplant follow-up includes monitoring of hematologic recovery, organ function, infection risk, and vaccination planning according to established transplant guidelines.

Ethics

This manuscript describes an institutional standard-of-care clinical protocol implemented within routine medical practice. As this work does not constitute an interventional research study and does not involve systematic data collection for research purposes, prior approval by a research ethics committee was not required under local institutional policies.

All patients undergoing AHSCT provide written informed consent for the procedure as part of routine clinical care, in accordance with national regulatory standards and the principles of the Declaration of Helsinki.

Any future secondary use of clinical data for research purposes will require submission to and approval by the appropriate research ethics committee, with informed consent obtained as applicable.

Because this manuscript describes an institutional standard-of-care protocol rather than an interventional clinical trial, it was not registered in a clinical trial registry platform.

DISCUSSION

AHSCT is an established high-efficacy option for selected patients with highly active inflammatory MS, particularly relapsing-remitting disease with ongoing clinical and MRI activity despite optimized HE-DMTs.[3] Randomized and observational data support deeper suppression of inflammatory activity and higher rates of durable remission, including sustained NEDA, compared with continued pharmacologic escalation in carefully selected RRMS populations.[8,20]

Safety has improved substantially with refinement of eligibility criteria, center experience, standardized supportive care, and intermediate-intensity conditioning approaches.[20] Aggregate evidence indicates that treatment-related mortality has declined to ~0.3% in studies published since 2005, with even lower rates reported in contemporary, highly selected RRMS cohorts, supporting the feasibility of AHSCT in experienced centers under structured multidisciplinary pathways.[3,16]

Economic considerations increasingly inform treatment sequencing. AHSCT is a one-time, time-limited intervention, whereas most HE-DMT strategies require indefinite administration, cumulative monitoring, and sustained expenditure. Comparative analyses suggest that AHSCT may become cost-effective over mid-term horizons, particularly when durable remission reduces the need for ongoing high-cost therapy.[12]

Implementation requires more than technical delivery. To reduce variability and support safe referrals, our protocol formalizes a neurology-to-transplant pathway with standardized referral criteria, multidisciplinary case conferences, defined pre-transplant requirements, and structured post-transplant neurological monitoring. As a single-center institutional protocol, this framework reflects local infrastructure and multidisciplinary expertise and may not be directly generalizable to all healthcare settings. However, by explicitly detailing selection, supportive care, infection surveillance (including viral monitoring), and multidimensional neurological outcomes, it provides a reproducible framework for quality assurance and real-world safety/effectiveness surveillance within routine clinical practice.

CONCLUSION

This manuscript presents a single-center institutional standard-of-care protocol for AHSCT in patients with highly active inflammatory RRMS in Brazil. By systematically defining eligibility criteria, mobilization strategy, conditioning regimen, supportive care measures, infection surveillance, and structured neurological follow-up, the protocol provides a transparent and reproducible clinical framework for AHSCT delivery within routine practice.

Through standardized patient selection and coordinated neurology-transplant collaboration, this framework supports safe implementation, consistent outcome monitoring, and alignment with contemporary international recommendations. Formalization of such care pathways may enhance risk mitigation, reduce practice variability, and contribute to the generation of high-quality real-world safety and effectiveness data in specialized centers.

CONFLICTS OF INTEREST

Nothing to declare.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

Artificial intelligence (AI) tools were used to assist in the graphical design and layout of the eligibility criteria figure. No AI tools were used for data analysis or scientific content generation.

FUNDING

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DATA AVAILABILITY STATEMENT

All datasets were generated or analyzed in the current study.

AUTHOR CONTRIBUTIONS

Conceptualization: Silva PDM, Vecino MCA. **Supervision:** Vecino MCA. **Writing:** Silva PDM, Abreu SJ, Vargas A. **Critical revision:** Silva PDM, Vecino MCA. **Final approval:** Silva PDM.

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