

Supplement 3 – Study Protocol

RESEARCH PROTOCOL

Hematopoietic stem cell transplantation for treatment of multiple sclerosis in Sweden

– a register-based retrospective observational study

Project Manager

Thomas Silfverberg, MD. Center for Clinical Research Dalarna/Department of Medical Sciences, Uppsala University

Principal investigator and scientific supervisor

Joachim Burman, MD, PhD. Ass Prof. of Neurology at the Department of Medical Sciences, Uppsala University

Entity responsible for the research

Department of Medical Sciences, Uppsala University, Region Uppsala

Date 2021-03-08

Title

Hematopoietic stem cell transplantation for treatment of multiple sclerosis in Sweden - a register-based retrospective observational study

Introduction

Multiple sclerosis (MS) is a debilitating disease affecting mainly young individuals, with a peak incidence around 30 years of age. In Sweden 20 000 persons suffer from MS and worldwide an estimated 2.5 million. MS is considered the most common cause of neurological disability in young adults.¹ Untreated, it often leads to severe disability and premature death.²⁻⁵ MS is considered an inflammatory and autoimmune disease of the central nervous system (CNS).

The cause of MS is unknown, but epidemiologic and genetic studies indicate that MS is triggered in genetically susceptible individuals following exposure to environmental factors. This eventually leads to loss of tolerance and activation of myelin-specific T cells. These auto-reactive immune cells will attack oligodendrocytes, resulting in myelin destruction, secondary axonal damage and neuronal loss. The course of MS is heterogeneous and usually involves an early, predominantly inflammatory disease phase of relapsing-remitting MS (RRMS). After a variable period, RRMS evolves into a progressively degenerative stage (secondary progressive MS, SPMS) with neurodegeneration, CNS atrophy and accumulation of disability.

Current treatments for MS aim to reduce inflammation in the CNS, but have several drawbacks. They have to be administered repeatedly, have potentially severe side effects (including death) and cannot suppress disease activity entirely. Moreover, they mainly benefit patients with RRMS and have very little effect once the neurodegenerative process has started. Approved treatments are expensive and constitute a heavy burden for the health care system.

Hematopoietic stem cell transplantation (HSCT) has been in use for treatment of malignancies since the 1950's.^{6,7} In 1990, Edward Donnall Thomas was awarded the Nobel Prize in Physiology or Medicine for the development of HSCT as a treatment for leukemia. The first transplantations were allogenic transplantations with graft from a donor. Autologous hematopoietic stem cell transplantation (AHSCT) was developed to restore remission or chronic phase in patients with advanced leukemia without a sibling donor. The breakthrough in its use came after finding circulating stem cells in peripheral blood in patients with chronic myeloid leukemia,^{8,9} which enabled a simplified method of harvesting hematopoietic stem cells. To harvest hematopoietic stem cells and then reintroducing them to the patients allowed for higher doses of chemotherapy to be administered, thus creating a deeper disease response. Since the 1980s AHSCT has become standard treatment in many lymphoid malignancies and some childhood solid tumors. One side effect of high dose chemotherapy and AHSCT is that the procedure resets the immune system leading to loss of acquired immunity including (most) memory cells.

In recent years, AHSCT has been utilized for treatment of autoimmune diseases such as MS. AHSCT aims to treat the disease to such a depth that remission is obtained and to remain in remission for as long as possible. For autoimmune diseases, the idea is to diminish the patients' immune system by depleting or eliminating mature lymphoid and myeloid cells with specific phenotypes in the adaptive immune system as well as changing the immunological environment. The procedure starts with harvesting the patients' hematopoietic stem cells by apheresis after mobilizing them from the bone marrow to the peripheral blood using a combination of the cytotoxic drug cyclophosphamide and granulocyte-colony-stimulating factor (G-CSF). The hematopoietic stem cells are identified by

expression of the surface molecule CD34 using immunophenotyping. The cells are then cryopreserved. 3-4 weeks later the patient is treated with high-dose chemotherapy referred to as *conditioning* that result in bone marrow aplasia. When the cytotoxic drugs has been eliminated from the body, the autologous CD34⁺ cells are reinfused to inhabit the empty bone marrow. In MS, the two most commonly used conditioning regimens are BEAM-ATG and Cy-ATG (see intervention below). The purpose of anti-thymocyte globulin (ATG) is to eliminate T-cells present in the graft. The patient becomes vulnerable for infections during the neutropenic phase following conditioning until engraftment, which normally occurs after 10-14 days. Consequently, the immune system is reconstituted with permanent and beneficial changes in the immune repertoire.

Current data suggest that the procedure is superior at maintaining a disease-free state in comparison to standard disease modifying drugs.¹⁰ At the same time, the safety profile seems to be acceptable, with a low rate of serious adverse events.¹⁰ As a first, the Swedish Board of Health and Welfare approved AHSCT for treatment of RRMS on the national level in 2016¹¹ and HSCT is now available as a therapeutic option in routine health care in Sweden.

Survey of the field

The first-generation trials investigating AHSCT for MS used heavy myeloablative transplantation regimens, which were associated with high treatment-related mortality. Additionally, the procedure was reserved for patients with treatment resistant progressive forms of MS. It soon became evident that this therapy was not able to stop worsening in patients with progressive disease.¹² In the following years, it became clear that HSCT could be a very effective treatment for RRMS.^{13,14} Development of less toxic conditioning regimens and better patient selection has led to a substantial decrease in treatment related mortality, which today has been estimated at 0.3%.¹⁵

In terms of efficacy, AHSCT compares favorably to conventional treatment. About two-thirds of treated patients reach complete remission with no evidence of disease activity (NEDA) 4-5 years after the procedure.¹⁶ With first line therapy, such as interferon beta, only 7.9 % had NEDA at seven years and even with strong immunosuppression, such as natalizumab or alemtuzumab, only 32-39 % of patients exhibited NEDA after a relatively short follow-up time of two years.¹⁷

The MIST-trial is the only randomized controlled trial investigating AHSCT vs disease-modifying treatment (DMT), such as natalizumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a, mitoxantrone, teriflunomide in MS-patients to this date. Interim results show a median time to progression of 24 months in the DMT arm compared to 1.92% of the patients in the AHSCT arm showing progression at 24 months.¹⁰ Although the procedure is expensive, it is a one-time treatment. When compared with conventional therapy in a cost-effectiveness analysis, the outcome is highly in favor of AHSCT.¹⁸

AHSCT has been shown to be more effective for treating RRMS than progressive MS in multiple trials. The current European Society for Blood and Marrow Transplantation (EBMT), the Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) points out that the use of AHSCT for primary progressive MS (PPMS) and secondary progressive MS (SPMS) is less effective compared to RRMS. According to the guidelines, AHSCT can be considered for progressive MS only if inflammatory activity is still evident but the benefit is considered very limited, especially for primary progressive MS (PPMS).^{19,20}

There has not been any randomized trials comparing conditioning regimens in MS. High intensity regimens such as busulfan + cyclophosphamide + ATG are associated with high risk for considerable toxicity including sinusoid obstruction syndrome.²¹ The two most commonly used regimens are the

intermediate intensity BEAM-ATG or Cy-ATG described previously. The current EBMT guidelines recommends both protocols.²⁰ A Brazilian retrospective study from 2009 compared the conditioning regimens BEAM + horse ATG (hATG) with cyclophosphamide + rabbit ATG (rATG) in 41 patients of which 80% had progressive MS. The study showed a mortality rate of 3 out of 21 treated patients in the BEAM-hATG cohort for patients treated between 2001 and 2004. The high mortality justified a change in the protocol to cyclophosphamide-rATG from 2004 to 2006 and there was no further treatment related mortality until the end of the follow up in late 2007. The overall adverse events were more common in the BEAM-hATG group.²²

Research question

What is the effectiveness and safety of autologous hematopoietic stem cell transplantation as treatment for relapsing-remitting multiple sclerosis?

Project Outline

This is an observational cohort study with retrospective analysis of prospectively collected data. The study cohort is constituted of all patients with relapsing-remitting multiple sclerosis treated with AHSCT in Sweden from 2004 when the first AHSCT was performed until 31 December 2019. The study aims to describe the effectiveness, safety and patient reported outcomes of AHSCT for MS through real world data. Treatment-related mortality will be analyzed from the start of mobilization until the end of the study. Other adverse events will be described until 3 months post-transplantation. A statistical subgroup comparison of efficacy and safety between the conditioning regimens BEAM-ATG and Cy-ATG will be included within the study.

Methodology

Study population

All individuals with a diagnosis of MS, who was treated with AHSCT in Sweden until 31 December 2019 can be included in this study. Patients will be identified through the local EBMT-registers and the Swedish MS register (SMSreg).

Inclusion criteria

- Diagnosis of multiple sclerosis according to the revised McDonald criteria 2017.²³
- Autologous hematopoietic stem cell transplantation performed for treating multiple sclerosis at a Swedish transplantation center until 31 December 2019.

Exclusion criteria

- Diagnosis of primary progressive MS or secondary progressive MS according to Lublin *et al*²⁴ at the time of transplantation.
- Patient not accepted reporting of data to the EBMT register.
- Not fulfilling requirements of the minimal dataset, see below.

Definition of minimal dataset

- Data on disease course of multiple sclerosis at the time of transplantation.
- Transplantation and the following in-patient care performed in Sweden.

- Date of transplantation.
- Data on drugs used in conditioning.
- At least one follow-up visit performed in Sweden* including data on:
 - Clinical assessment
 - The Kurtzke Expanded Disability Status Scores (EDSS)

*Unless early death before first follow-up visit.

Additional note: For a patient to be included in the analysis of treatment effectiveness data on MRI evaluation is needed at least once during follow-up.

Intervention

The therapeutic intervention of AHSCT consists of four parts: the mobilization of hematopoietic stem cells (HSC), the harvest of HSCs, the ablation (conditioning) of the immune system and the reinfusion of autologous HSCs.

In Sweden a combination of cyclophosphamide (2 g/m^2) and G-CSF is used to mobilize the HSCs. The HSCs are identified by immunophenotyping, and cells that express CD34 on their surface are considered to be HSCs. A minimum of 2×10^6 CD34⁺ cells/kg is harvested and then cryopreserved. No in vitro manipulation is done to the stem cells.

After a few weeks, conditioning is performed with high-dose chemotherapy. The two dominating protocols for conditioning in Sweden are BEAM-ATG and Cy-ATG. The BEAM-ATG protocol consists of carmustine (BCNU) 300 mg/m^2 , etoposide 800 mg/m^2 , cytarabine arabinoside (ARA-C) 800 mg/m^2 and melphalan $140 \text{ mg/m}^2 + \text{rATG}$ or hATG. The Cy-ATG protocol include cyclophosphamide $200 \text{ mg/kg} + \text{rATG/hATG}$ with 1000 mg Methylprednisolone given day -5 to -1 and Mesna given repeatedly to avoid hemorrhagic cystitis. High-dose steroids and hyperhydration is used in most Swedish centers when giving high-dose cyclophosphamide conditioning.

After a minimum of 24 hours after the last administration of chemotherapy have passed, the reinfusion of autologous CD34⁺ cells is made. Prophylaxis for bacterial infection with the quinolone ciprofloxacin is given during the neutropenic phase. Additional antibiotics may be administered as needed. Filtered and radiated blood products are used until their lymphocytes exceeds $1,0 \times 10^9/\text{L}$. Prophylaxis for herpes and pneumocystis is given for a minimum of 3 months. Prophylaxis for hepatitis B-reactivation is given to patients who has tested positive for HBs-ag (hepatitis B surface antigen) and/or anti-HBc (antibodies against hepatitis B core proteins).

Source data verification

To verify the accuracy and completeness of data in EBMT and SMSreg, a verification of source data *vis-à-vis* the medical records will be made by local co-principal investigators.

Data collection

Baseline data on birth date, sex, date of onset, date of diagnosis, disease course, previous treatments, etc. will be collected from the SMSreg (see data points below).

Data on the circumstances of the intervention will be collected from local repositories of the EBMT and supplemented by reviews of the medical records. This includes data points such as doses and

names of drugs used for mobilization and conditioning, dates for administration of these drugs, date of hematopoietic stem cell transplantation, date of hematological milestones, occurrence and grading of adverse events during the first three months after the intervention.

Data on clinical outcome after the first three months of the intervention will be collected from SMSreg. Apart from mortality, long-term complications including autoimmune disease will not be analyzed in this study, since that has already been published in a different study.²⁵ Mortality at any point after AHSCT will be analyzed through the medical records to determine if it was treatment-related. Data on treatment related mortality will be analyzed until the time of data collection.

Data management

All data collected will be stored in a deidentified data set where name and social security number have been erased and given a coded study number (pseudonym). The data set will be stored at a secure server belonging to the entity responsible for the research. Each patient will only be identified using a separately and securely stored code key only available to the main researchers. All storage, correspondence and analysis with the pseudonymized data set will adhere to current European General Data Protection Regulation (GDPR) guidelines. The code key will be stored until the study is published, not exceeding two years after the end of the data collection, to allow for any relevant data additions and then be destroyed. The data set will be stored for 15 years and then be destroyed.

Ethical Review Authority approval

Approval from the Swedish Ethical Review Authority is pending.

Definitions

Annualized relapse rate (ARR)

The number of relapses occurring during a time period divided by the number of years in that time period. E.g. 5 relapses occurring in a time period of 2.5 years equals an ARR of 2 ($5/2.5=2$).

Clinical improvement

Baseline EDSS ≤ 5.5

A decrease in EDSS score with at least 1 point from baseline that is sustained between two follow-up visits separated in time by no less than six months.

Baseline EDSS ≥ 6

A decrease in EDSS score with at least 0.5 points from baseline that is sustained between two follow-up visits separated in time by no less than six months.

Clinically isolated syndrome (CIS)

According to the Lublin *et al* criteria from 2014.²⁴

Clinical progression

Baseline EDSS ≤ 5

An increase in EDSS score with at least 1 point from baseline that is sustained between two follow-up visits separated in time by no less than six months.

Baseline EDSS ≥ 5.5

An increase in EDSS score with at least 0.5 points from baseline that is sustained between two follow-up visits separated in time by no less than six months.

EDSS

The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. The EDSS is a composite of disability in eight functional systems.

FSMC

Fatigue Scale for Motor and Cognitive Functions (FSMC) is a 20-item scale for evaluating MS-related cognitive and motor fatigue.²⁶

MRI progression

The appearance of any T2 lesion > 3 mm or gadolinium enhancing lesion in the brain or spinal cord not present on the baseline scan.

MSIS-29

The Multiple Sclerosis Impact Scale (MSIS-29) is a measure of the physical and psychological impact of MS from the patient's perspective.²⁷

Multiple sclerosis, diagnosis

Diagnosis according to the revised McDonald Criteria from 2017.²³

No evidence of disease activity (NEDA)

'No evidence of disease activity' is defined as absence of relapses in addition to absence of clinical progression and MRI progression.

Primary Progressive multiple sclerosis (PPMS)

According to the Lublin *et al* criteria from 2014.²⁴

Progressive disease

According to the Lublin *et al* criteria from 2014.²⁴

Relapse

A period of acute worsening of neurological function lasting ≥ 24 hours not attributable to an external cause such as increased body temperature or acute infection.

Relapsing/remitting multiple sclerosis

According to the Lublin *et al* criteria from 2014.²⁴

Treatment related mortality (TRM)

TRM is defined as death due to any transplantation-related cause other than disease progression.

SDMT

Symbol Digit Modalities Test (SDMT) is a test of cognitive function in MS-patients.²⁸

Data points

Baseline data

Birth date, clinical course (RRMS, SPMS or PPMS), disease onset, diagnosis date, previous disease modifying drug (DMD) treatments, number and dates of relapses prior to HSCT, results and dates of MRI investigations prior to HSCT, results and dates of EDSS scoring prior to HSCT. Wash-out period prior to AHSCT.

HSCT data

Transplant date, type of mobilization, conditioning, dosage, days to engraftment, days to discharge, intensive care (yes/no), reactivation of CMV, EBV or other herpes viruses, bacteremia (species), culture negative fever, hemorrhagic cystitis (yes/no) and other serious adverse events grade three or higher according to the NIH common terminology criteria for adverse events (CTCAE).

Follow-up data

Number and dates of relapses after HSCT, results and dates of MRI investigations after HSCT, results and dates of EDSS, FSMC, MSIS-29 and SDMT scoring after HSCT, serious adverse events grade three or higher according to CTCAE until day +100, subsequent DMD treatment.

Endpoints

Recently a survey of Swedish MS patients was made to investigate which aspects of DMD treatment were most important to them. Two of the outcomes that were ranked highest were long-term disability and risk of serious adverse events. The endpoints of this study were deliberately chosen to assess these outcomes.

Primary endpoints

- The Kaplan-Meier estimate of NEDA at five years.
- Treatment related mortality

Secondary endpoints

- The Kaplan-Meier estimate of NEDA at three and ten years.
- The Kaplan-Meier estimate of MRI event free survival at three, five and ten years.
- The Kaplan-Meier estimate of Relapse free survival at three, five and ten years.
- The Kaplan-Meier estimate of Progression free survival at three, five and ten years.
- The annualized relapse rate (ARR) after AHSCT.
- The proportion of patients with clinical improvement.
- The EDSS change between baseline and follow-up at one, two and three years respectively.
- The frequency and grade of serious adverse events within 100 days

Explorative endpoints

- Changes in cognitive function, measured by SDMT at one, two and three years
- Changes in quality of life, measured by MSIS-29 at one, two and three years.
- Changes in MS-related fatigue, measured by FSMC at one, two and three years.

Data analysis

The endpoints will be analysed and described for the whole study cohort. Subgroup analysis comparing BEAM-ATG and Cy-ATG will be conducted to statistically analyse if there are any significant differences in between the two conditioning regimens in terms of efficacy and safety. The explorative endpoints will be analysed if the quality of the data is good enough, as the coverage of these data points in the SMSreg are not known.

Aggregated data will be reported as frequencies for categorical variables and medians with interquartile intervals for continuous variables. The Wilcoxon signed rank test will be used to establish statistical significance between two time points and the Friedman test will be used to establish statistical significance between three or more time points. Survival at different time points will be estimated with Kaplan–Meier survival curves and statistical significance will be established with the log-rank test. A two-tailed p value of < 0.05 will be considered to be statistically significant.

Reporting of data

Reporting of the data will adhere to the STROBE guidelines. Open access will be granted to the reported data.

Work plan

- Q3 2021 Start of collection of data
- Q1 2021 Completion of collection of data.
- Q2 2022 Start of data analysis
- Q3 2022 Completion of data analysis.
- Q4 2022 Final report

Importance

HSCT is a potentially curative treatment of RRMS and leads to long-term remission in a majority of patients. It has so far not been possible to estimate effectiveness and safety on a large scale, due to its limited use and the heterogeneity of previous reports. In the last years, AHSCT has seen increasing use in Sweden and the Swedish Board of Health and Welfare recently endorsed it. This study of real world data that aims to provide a general picture of the effectiveness and safety of AHSCT for RRMS. The data analysis will include some outcome measures that were identified as of particular importance by stakeholders, such as fatigue. As a result of the excellent coverage of the national SMSreg a minimum of patients will be lost to identification and follow-up, thus providing strength to the report. As this study describes a treatment option, the research question concerns the patients directly and the hypothesis is that the treatment is relatively safe, economically advantageous and effective for treating RRMS. The proposed study will be the largest study of HSCT for RRMS so far, with a size that is equal to all of the previous reports combined. We will be able to estimate the level of serious adverse events on a level of detail that has not been possible before. Thus, the results of this study will be able to provide new and important information, which will enable health care providers and patients to make a better-informed treatment choice. The study will also provide deeper insight in the comparison between the currently two most widely used conditioning regimens used for MS.

Main participants

Project Manager

Thomas Silfverberg, MD (Center for Clinical Research Dalarna/Department of Medical Sciences, Uppsala University)

Principal investigator and scientific supervisor

Joachim Burman, MD, PhD. Ass Prof. of Neurology at the Department of Neuroscience, Uppsala University

References

1. Compston A, Coles A. Multiple sclerosis. *The Lancet*. 2002;359(9313):1221-1231.
2. Brønnum-Hansen H K-HN, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain*. 2004;127(Pt 4):844-850.
3. Daumer M, Griffith LM, Meister W, Nash RA, Wolinsky JS. Survival, and time to an advanced disease state or progression, of untreated patients with moderately severe multiple sclerosis in a multicenter observational database: relevance for design of a clinical trial for high dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation. *Multiple Sclerosis*. 2006;12(2):174-179.
4. Hader W. Disability and survival of multiple sclerosis in Saskatoon, Saskatchewan. *Can J Neurol Sci*. 2010;37(1):28-35.

5. Skoog B, Runmarker B, Winblad S, Ekholm S, Andersen O. A representative cohort of patients with non-progressive multiple sclerosis at the age of normal life expectancy. *Brain : a journal of neurology*. 2012;135(Pt 3):900-911.
6. W. MF, Granville NB, Dameshek W. Autologous bone marrow infusion as an adjunct in therapy of malignant disease. *Blood*. 1959;14(5):503-521.
7. Thomas ED, Lochte HL, Jr., Cannon JH, Sahler OD, Ferrebee JW. Supralethal whole body irradiation and isologous marrow transplantation in man. *The Journal of clinical investigation*. 1959;38:1709-1716.
8. Philip T, Armitage JO, Spitzer G, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med*. 1987;316(24):1493-1498.
9. Reiffers J, Trouette R, Marit G, et al. Autologous blood stem cell transplantation for chronic granulocytic leukaemia in transformation: a report of 47 cases. *Br J Haematol*. 1991;77(3):339-345.
10. 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):165-174.
11. Vård vid multipel skleros och Parkinsons sjukdom. In: Welfare SBoHa, ed2016:26-30.
12. Burt RK, Cohen BA, Russell E, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. *Blood*. 2003;102(7):2373-2378.
13. Fagius J, Lundgren J, Oberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation. *Mult Scler*. 2009;15(2):229-237.
14. Burt R, Loh Y, Cohen B, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. *Lancet Neurol*. 2009;8(3):244-253.
15. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis. *Neurology*. 2017;88(22):2115-2122.
16. Sormani MP, Muraro PA, Saccardi R, Mancardi G. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. *Mult Scler*. 2017;23(2):201-204.
17. Rotstein DL, Healy BC, Malik MT, Chitnis T, Weiner HL. Evaluation of No Evidence of Disease Activity in a 7-Year Longitudinal Multiple Sclerosis Cohort. *JAMA neurology*. 2014.
18. Tappenden P, Saccardi R, Confavreux C, et al. Autologous haematopoietic stem cell transplantation for secondary progressive multiple sclerosis: an exploratory cost-effectiveness analysis. *Bone Marrow Transplant*. 2010;45(6):1014-1021.
19. Muraro PA, Pasquini M, Atkins HL, et al. Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. *JAMA neurology*. 2017;74(4):459-469.
20. 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.
21. Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. *Lancet*. 2016;388(10044):576-585.
22. Hamerschlag N, Rodrigues M, Moraes DA, et al. Brazilian experience with two conditioning regimens in patients with multiple sclerosis: BEAM/horse ATG and CY/rabbit ATG. *Bone Marrow Transplant*. 2010;45(2):239-248.
23. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
24. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. 2014.
25. Alping P, Burman J, Lycke J, Frisell T, Piehl F. Safety Outcomes after Alemtuzumab and AHSCT in Patients with Multiple Sclerosis: A Cohort Study. *Neurology*. 2021.
26. Penner IK, Raselli C, Stocklin M, Opwis K, Kappos L, Calabrese P. The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler*. 2009;15(12):1509-1517.
27. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain*. 2001;124(Pt 5):962-973.
28. Benedict RH, DeLuca J, Phillips G, et al. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Mult Scler*. 2017;23(5):721-733.