Autologous Hematopoietic Stem Cell Transplantation in Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic, inflammatory and immune-mediated disease of the central nervous system (CNS), commonly affecting young adults and potentially associated with life-long disability. About 14 disease-modifying treatments (DMTs) are currently approved for the treatment of MS. Autologous Hematopoietic Stem Cell Transplantation (AHSCT) is a highly efficacious and relatively safe therapeutic option for the treatment of highly active MS. Particularly, over recent years, the amount of evidence has grown, with significant improvements in the development of patient selection criteria, choice of the most suitable transplant technique and clinical experience.

hematopoietic stem cell transplantation | treatment | multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, neurodegenerative and immune-mediated disease of the central nervous system (CNS) characterized by inflammatory demyelination and subsequently gliosis and axonal loss [1][2].

Over the last two decades, thanks to the growing knowledge about MS pathogenesis, a fair amount of disease-modifying therapies (DMTs) have been developed for the treatment of MS. These drugs have different mechanisms of action directed to control the inflammatory component of the disease, with the result of reducing the risk of relapse and the accumulation of the disability [2]. To date, a total of 14 DMTs have been approved with different efficacies and safety profiles. Despite their use, many patients remain at some risk for relapses and disability progression; in particular, those exhibiting a severe disease activity despite the use of highly active treatment or showing an aggressive course from disease onset are exposed to a high risk of long-term disability accrual [3]. In these cases, autologous hematopoietic stem cell transplantation (AHSCT) can be considered as a possible therapeutic option. AHSCT has been employed to treat MS over the last two decades and, unlike most of the currently approved DMTs, it was originally applied in hematologic settings and, since the 1990s, has been used to treat refractory autoimmune diseases [4].

2. Safety of AHSCT in Multiple Sclerosis

The main AHSCT-related complications in MS are illustrated in **Table 1**.

Table 1. AHSCT-related complications commonly associated with MS patients.

	MS Risk Factor	Measure to Prevent/Treat
Early AEs		
ATG fever [5][6]	Cytokine release	Steroids, antipyretics
Worsening of neurological symptoms [5][6][7]	Fever	Treat cause of fever
LUTS [6][7]	Neurologic bladder	Antimicrobials Rehydration
Hemorrhagic cystitis [5][6][7]	Neurologic bladder	Urinary catheter, rehydration
EBV/CMV reactivation [5][6][7]	Previous exposure to EBV/CMV	Monitoring of EBV/CMV DNA
Pneumonia [5][6][7]	Muscular weakness, immobility	Antimicrobials, early mobilization
Deep vein thrombosis [6][7]	Immobility	Early mobilization, anticoagulants
Falls [5]	Muscular weakness, dehydration	Physiotherapy, fluid monitoring
Late AEs		
PML [8][9][10]	Positive antibodies against JCV, previous treatment with natalizumab	Wash-out after the withdrawal of natalizumab, JCV testing prior to the AHSCT procedure
Varicella zoster reactivation [11]	Immunosuppression	Antiviral prophylaxis
Secondary autoimmune diseases [12][11][5][13][14][15]	Pretreatment with ALM or ATG	Close follow-up
Premature menopause and infertility [16][15][17][18]	Older age, high intensity of the conditioning regimen	Counseling, adoption of fertility preservation strategies
Malignancies [19][20][21][22][23][24][5][25] [26][27][28]	Allogeneic HSCT, previous use of immunosuppressive drugs	Close follow-up

2.1. Early Complications

AHSCT: autologous hematopoietic stem cell transplantation; AE: adverse event; ALM: alemtuzumab; ATG: anti-thymocyte globulin; EBV: Epstein–Barr virus; CMV: cytomegalovirus; JCV: John Cunningham virus; GI: gastrointestinal; UTIs: lower urinary tract infections; MS: multiple sclerosis; PML: progressive multifocal leukoencephalopathy.

The AHSCT procedure includes the administration of cytotoxic chemotherapy that may cause several common adverse effects (AEs), such as anaphylactic reactions, neutropenic fever, infections and sepsis, gastrointestinal toxicity and symptoms, viral reactivations (particularly Epstein–Barr virus (EBV), cytomegalovirus, varicella zoster virus, etc.) [5][6][7].

Neutropenic fever and/or sepsis require immediate assessment, clinical examination and a prompt therapeutic approach with antibiotics; in case this condition significantly persists even beyond the conditioning phase, it should also be evaluated whether it could be related to the effect of AHSCT. Corticosteroids and paracetamol may help to prevent prolonged pyrexia when the presence of infections is excluded [5]. Moreover, peri-transplant-sustained pyrexia, aside from being a possible infective cause, correlated with poor long-term neurological recovery [5]. Indeed, patients who underwent AHSCT may experience a transient neurological worsening; in particular, fever secondary to the AHSCT and/or to infection may worsen neurological symptoms, such as spasticity, pain, urinary symptoms, weakness and fatigue. For this reason, therapeutic interventions should be promptly carried out to prevent prolonged pyrexia, whatever might be the cause.

2.2. Late Complications

One of the most common late complications of AHSCT is the reactivation of the varicella zoster virus, possibly secondary to the significant immunosuppression related to the conditioning regimen [11].

Among viral reactivations, progressive multifocal leukoencephalopathy (PML), a severely disabling and potentially life-threatening disease caused by the reactivation of John Cunningham virus (JCV), mainly in immunosuppressed patients, has raised concerns in the last decade as a potential adverse event of several DMTs, particularly natalizumab [8][9][10]. According to the current literature, only one case of PML has been reported 11 years after an AHSCT in a patient who had received natalizumab treatment for about 3 years, and thus, it could not be considered as related to the AHSCT [28]. Therefore, to date, no cases of PML associated with AHSCT have been reported so far in MS patients. However, the PML risk could be mitigated by adopting adequate wash-out periods after the discontinuation of highly active DMTs potentially at risk of PML and/or dosing the titer of antibodies against JCV prior to the AHSCT procedure.

Following AHSCT, a higher percentage of MS patients compared to the oncologic setting exhibits secondary autoimmune diseases, such as autoimmune thyroiditis, immune thrombocytopenic purpura (ITP), rheumatoid arthritis, Crohn's disease and acquired anti-factor VIII inhibitor diseases [12][11][13][29]. In a retrospective analysis of patients from the EBMT and Center for International Blood and Marrow Transplant Research (CIBMTR) databases, the incidence of autoimmune AEs mainly consists of thyroiditis, with 5% over a median follow-up of 6.6 years after AHSCT [12][14]. Higher rates (26% and 23%) were reported in a subgroup of patients who had performed the ex vivo manipulation of the graft and in a cohort who had received a conditioning regimen that included alemtuzumab, respectively [11][5].

However, patients treated with alemtuzumab showed higher rates of autoimmune AEs compared to those receiving AHSCT, with almost half of the patients developing a secondary autoimmune condition at 2 years from the second alemtuzumab course [30].

Long-term potential AEs also include effects on fertility and the occurrence of malignancies. For female patients of childbearing potential who underwent AHSCT, the high risk of premature menopause and infertility represents a relevant concern. The risk is significantly associated with the age at transplant, with patients older than 30 years showing the highest risk, and the intensity of the conditioning regimen [31]. Nevertheless, a retrospective analysis of 324 women treated with AHSCT for autoimmune diseases reported 15 pregnancies, 11 of them terminated with 7 healthy live births [15].

A multicenter study reported on post-AHSCT menstrual resumption in 43 MS female patients showing that 30 (70%) started menstruating again after a mean time of 6.8 months [17].

Moreover, in a phase 2 trial of AHSCT for MS, out of 55 patients enrolled, 33 were women and had undergone AHSCT while being of childbearing age at the time of the AHSCT procedure. In a study reporting the outcomes of four pregnancies that occurred after AHSCT, two of them were carried to term with no maternal or neonatal complications. The remaining were not carried to term due to elective termination. Out of 21 males enrolled, one patient has fathered three children since his AHSCT. No newborn complications were reported [18].

Data about male fertility after AHSCT are scarce; however, AHSCT seems to only minimally affect reproductive functions. A small study that enrolled four males who underwent a procedure with Cy and ATG for autoimmune diseases showed a reduction in testosterone compared with baseline values. However, the levels of testosterone remained within the normal range in three patients [16]. Potential complications on the reproductive functions and the possible adoption of fertility preservation strategies should be extensively discussed with patients who are potentially eligible for AHSCT.

Few studies have described the occurrence of tumors following AHSCT. In a recent retrospective study, malignancies were diagnosed in 3.2% of patients (9 of 281 treated patients) [12]. In this analysis, with the exception of three cases of myelodysplastic syndromes typically associated with exposure to cytotoxic drugs, no organ-specific prevalence was detected [12]. Moreover, in the current literature, six malignancies occurred, where one of them was reported in a patient treated with DMT after AHSCT [5][25][28]. Notably, an increased risk of malignancies was reported in patients who received allogeneic HSCT (allo-HSCT) [32]. Similarly, some studies suggested that treatments received prior to AHSCT might play a role in the global cancer risk as MS patients treated with immunosuppressive drugs were more at risk of malignancies, possible due to a reduction in immunosurveillance [33][34].

The risk of mortality represents the main concern limiting the use of AHSCT for MS treatment. Procedures performed between 1995 and 2000 showed transplant-related mortality of 7.3%, 1.3% between 2001 and 2007 and 0.7% between 2008 and 2016, with a dramatic decline in the last decade, where it progressively reduced to 0.2%

(1/439) [35]. Across the studies, overall mortality was 2.0% in 829 MS patients transplanted and 2.8% of 281 treated in two retrospective studies [4][12]. A higher rate (4%) was reported in another study; in this analysis, one of the 24 deaths was attributed to hepatic necrosis following busulfan-related sinusoidal obstruction syndrome. Thereafter, during the study, in order to reduce regimen-related toxicity, the dose and route of administration of busulfan were changed [11]. In most of the remaining studies, the mortality was 0% [19][20][21][22][23][24][5][25][26][27][28]. According to recent meta-analyses, patients with specific clinical and demographic features, such as higher disability at baseline, older age and a non-RRMS course, were associated with higher mortality risk [36][37][38]. Moreover, high intensity of the conditioning regimens was associated more frequently with higher rates of mortality (3.13% for high vs. 0.97% for low-to-intermediate intensity). Interestingly, patients who received AHSCT before 2006 were at higher risk, with a significant chronological improvement in the more recent 5-year epochs from 1994 to 2015, probably thanks to a better selection of eligible patients and improving expertise of transplant centers [38].

2.3. COVID-19

In the last two years, coronavirus infectious disease (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has become a pandemic threatening global health, as well as affecting the therapeutic management for MS [39]. During the pandemic, a retrospective Italian study found that most of the currently used DMTs were acceptably safe, bringing out some specific elements of risk concerning the use of anti-CD20 drugs [40]. COVID-19 has a great impact on HSCT activity worldwide; the EBMT has, therefore, developed recommendations for transplant programs and physicians caring for these patients [41]. Patients receiving AHSCT for hematological diseases showed a protracted duration of COVID-19 symptoms and a higher risk of generation of highly mutated viruses. Moreover, several studies demonstrated a higher risk of COVID-19 mortality in patients receiving HSCT; however, older age, the presence of comorbid conditions and the immunosuppression due to both treatments and underlying hematological malignancy may also contribute to a more severe COVID-19 course [42]. Particularly, the mortality rate was 11.5% in patients who were not treated with immunosuppressive drugs at the time of COVID-19 diagnosis, while it rose to 33% in those who were immunosuppressed [43].

In the MS setting, not enough data are available in order to define the risk profile of AHSCT during the COVID-19 pandemic. However, reports from the current literature do not suggest a more severe course and higher mortality rates in MS patients who have received AHSCT and faced SARS-CoV-2 infection [40].

3. Autologous Hematopoietic Stem Cell transplantation and Vaccination

To the best of researchers' knowledge, no data are available about the effect of AHSCT on vaccination response in MS [44]. However, even considering patients receiving transplants for hematological diseases, the literature is scarce and consensus on the timing of post-hematopoietic stem cell transplantation vaccination is currently lacking. In a recent review, it was reported that patients receiving allo-HSCT had a 12 months post-transplant response to influenza vaccine of over 45% that ranged between 10 and 97% at 7–48 months. The response to pneumococcal vaccination at 3–25 months post transplant was 43–99%, increasing over time. For diphtheria, tetanus, pertussis,

poliomyelitis and Hemophilus Influenzae type b vaccinations the response ranged from 26 to 100% after 6–17 months from the transplant. The rate of response after meningococcal vaccination at 12 months post transplant was 65%; whilst the hepatitis B vaccine at 6–23 months produced a response in 40–94%. Similarly, measles, mumps and rubella vaccinations at 41–69 months post transplant showed a response in 19–72%. In general, in patients receiving AHSCT, the responses were slightly higher when compared with allo-HSCT [45].

Initial reports on the antibody response after full SARS-CoV-2 vaccination in hematological patients showed that antibody response rates were lower compared with the healthy population. In a prospective study of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC) on a large cohort of patients with different diseases (most of them with onco-hematological conditions), 242 (78%) of patients who received allo-HSCT and 73 (85%) of those who have received AHSCT showed detectable SARS-CoV-2-reactive antibodies [46]. Most patients received mRNA-based vaccines and were vaccinated more than 1 year after transplantation [46].

4. Factors Influencing the Success of AHSCT and Choice of Conditioning Regimen

Several baseline characteristics were identified as predictive factors for the AHSCT outcome. Some studies demonstrated that a progressive phenotype was associated with a higher risk of post-AHSCT progression (HR 2.33, 95%CI 1.27–4.28) compared with relapsing MS [12][5][25][47]. On the other hand, short disease duration, younger age at the time of the AHSCT and a lower number of previous DMTs correlated with a positive outcome [12]. This was confirmed by a recent retrospective study in which 20 patients with “aggressive” MS underwent AHSCT as a first therapeutic choice. After a median follow-up of 30 (12–118) months, the median EDSS score markedly reduced from 5.0 (1.5–9.5) at baseline to 2.0 (0–6.5), and no patient exhibited further relapses. MRI showed residual disease activities in three patients during the first 6 months after AHSCT, while no further new or enhancing lesions were detected in subsequent scans [48].

In general, these studies contribute toward providing an outline of the “ideal candidate” profile for the AHSCT, suggesting that younger age, highly inflammatory-active MS, mild disability progression and no multiple treatments failure are distinctive elements of better outcomes in terms of efficacy and safety profile following AHSCT [4].

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