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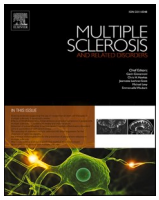

Review article

Should autologous hematopoietic stem cell transplantation be offered as a first-line disease modifying therapy to patients with multiple sclerosis?

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ABSTRACT

In multiple sclerosis (MS), progression independent of new focal inflammation may commence shortly after disease onset, and it is increasingly revealed that the risk of disability accrual is reduced by early use of high-efficacy disease-modifying therapies (HE-DMTs). People with aggressive MS may therefore benefit from early treatment with autologous haematopoietic stem cell transplantation (AHSCT), a procedure inducing maximal immunosuppression followed by immune reconstitution, demonstrated to be superior to DMTs in one randomized clinical trial. However, in current practice prior failure to HE-DMTs is typically required to establish the indication for AHSCT. In the present article, the available evidence on the potential role of AHSCT as first-line treatment in aggressive MS and the rationale for its early use will be summarized. Proposed definitions of aggressive MS that could help identifying MS patients eligible for early treatment with AHSCT will also be discussed.

1. Introduction

Multiple sclerosis (MS) is an autoimmune demyelinating and degenerative disease of the central nervous system (CNS) with typical onset in young adults, that represents a relevant socio-economic burden (Thompson et al., 2018). The course of MS at disease onset is relapsing-remitting (RR) in approximately 85% of the cases, being characterized by the occurrence of acute or subacute episodes of neurological symptoms (relapses) that may resolve completely, or with a residual deficit (Lublin et al., 2014). After a variable amount of time, people with MS (pwMS) may turn from RR to secondary-progressive (SP) MS, a stage characterized by disability accrual mostly independent of new focal inflammatory activity, with sparse relapses or newly developed magnetic resonance imaging (MRI) lesions (Lublin et al., 2014).

MS has traditionally been regarded as a two-stage disease, with different pathogenetic mechanisms dominating each phase: disease activity and disability accrual were considered to be predominantly driven by acute (adaptive) inflammation during early (RR) MS, whereas in later stages (SPMS) disability was mainly determined by chronic inflammation and degenerative processes, the latter considered mostly independent from inflammation (Lassmann, 2018; Leray et al., 2010). In this view, the window of therapeutic opportunity was placed in the early inflammatory phases, where the administration of disease-modifying therapies (DMTs) was expected to affect disease course and delay the achievement of disability milestones (Coles et al., 2006). Over the last two decades, the early use of DMTs, especially of high-efficacy (HE-) DMTs (i.e. natalizumab, anti-CD20 monoclonal antibodies, and alemtuzumab), may indeed have contributed to the apparent more benign course of MS (Sorensen et al., 2020).

Despite treatment with HE-DMTs, breakthrough disease activity is observed in a subset of pwMS, and may require treatment escalation. Such patients might have been considered eligible for autologous haematopoietic stem cell transplantation (AHSCT), a well-established medical procedure for the treatment of aggressive onco-haematological diseases and also used since the late Nineties for the treatment of pw severe autoimmune diseases refractory to conventional therapies (Muraro et al., 2017a). Up to December 2022, 2101 pwMS have been treated with AHSCT and registered in the European Blood and Marrow Transplantation Society (EBMT) database (Greco, 2023). On the grounds of increasing evidence of its efficacy and safety in MS (Burt et al., 2019), AHSCT was endorsed as a "standard of care" for

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treatment-refractory RRMS by the EBMT and the American Society for Blood and Marrow Transplantation (Cohen et al., 2019; Sharrack et al., 2019). Due to different safety profile involving higher upfront risks compared with conventional DMTs, the use of AHSCT has been restricted to pwMS who had failed conventional treatments, including at least one HE-DMT in most protocols eligibility criteria. However, the use of AHSCT has also been explored as a "first-line" treatment in a few pwMS presenting poor prognostic factors (Das et al., 2021).

In the present paper, we will discuss the rationale for the use of AHSCT in treatment-naïve pwMS and potential inclusion criteria, and we will review the published clinical experience.

2. Rationale for the use of AHSCT in early MS

Currently available DMTs mainly target the adaptive immune system and are most effective when administered in the early phase of MS (Chalmer et al., 2018). Although different DMTs reduce, to a variable extent, new focal inflammatory events (relapses, and new/gadolinium-enhancing lesions at MRI), their efficacy in halting disability accrual is overall moderate, especially in progressive disease (Hauser and Cree, 2020). Furthermore, the notion of progression independent of relapse activity (PIRA) since early RRMS (Portaccio et al., 2022; University of California et al., 2019) challenges the classic paradigm of MS as a two-stage disease, suggesting that a DMT-resistant pathology may set in from the start (Lublin et al., 2022). The progressive loss of neurological reserve due to MS-related inflammation was also suggested to play a role in the onset of progressive MS (Vollmer et al., 2021). These observations raise the questions whether the window of therapeutic opportunity for HE-DMTs should be further anticipated (Filippi et al., 2022) and whether available DMTs can halt PIRA or not.

Recent registry-based and cohort studies show that, at a population level, early treatment (i.e. within two years from clinical MS onset) with HE-DMTs reduced the hazard of long-term progression compared to late treatment (i.e. 4–6 years after disease onset) (He et al., 2020) by 54% and that escalation strategy was less effective on disability outcomes than early intensive treatment (Harding et al., 2019). Accordingly, the use as a first-line treatment of HE-DMTs reduced the risk of disability accrual compared to moderate-efficacy DMTs (Buron et al., 2020) and of conversion to SPMS compared with initial treatment with glatiramer acetate or interferon beta (Brown et al., 2019).

Besides disease duration, age strongly influences MS phenotype and treatment response (Scalfari et al., 2016; Signori et al., 2015). In a meta-analysis of 28,000 pwMS enroled in trials of immunomodulatory treatments, HE-DMTs outperformed low-efficacy drugs in inhibiting MS disability only for patients younger than 40.5 years, reinforcing the role of age as an essential modifier of drug efficacy (Weideman et al., 2017).

Against this background, it is reasonable that, in highly selected patients, early use of AHSCT may offer advantages over alternative DMTs. Superior effectiveness of AHSCT over DMTs on relapses, disability and no evidence of disease activity (NEDA) status was demonstrated in RRMS by the randomized clinical trial (RCT) MIST, although the comparator arm was a mixture of moderate and high-efficacy therapies (Burt et al., 2019). With respect to HE-DMTs, a post-hoc analysis from the same trial suggested possible superior effectiveness of AHSCT over natalizumab. At year 3, in the natalizumab-treated cases ($n = 19$) the rates of EDSS worsening, relapses, and NEDA were 30.5%, 75.4%, and 12.6% respectively, compared to 5.2, 9.6, and 90.3% of AHSCT-treated patients respectively. No head-to-head comparisons between AHSCT and HE-DMTs other than natalizumab are available to date. Retrospective studies suggested superiority of AHSCT over alemtuzumab on relapses, NEDA, MRI activity and disability improvement (Boffa et al., 2020; Häußler et al., 2021; Zhukovsky et al., 2021), but not on EDSS worsening, except in one study (Zhukovsky et al., 2021). However, no statistical matching between patients receiving either treatment was performed, resulting in significant differences between groups on baseline variables as well as on follow-up duration, generally longer for AHSCT compared to alemtuzumab groups. More recently, a registry-based study compared outcomes in RRMS patients treated with AHSCT with propensity score-matched controls who received fingolimod, ocrelizumab or natalizumab selected from the MSBase Registry (Kalincik et al., 2023). Over 5 years, AHSCT was associated with a lower risk of relapses and a higher chance of disability improvement compared with fingolimod and natalizumab, without significant differences in disability worsening. Over 3 years, the observed rates of relapses and disability worsening / improvement were similar between AHSCT and ocrelizumab; however, the follow-up for ocrelizumab-treated cases was short (mean 1.5 years). Further limitations of the study included use of different AHSCT protocols, possible residual heterogeneity in patient populations, lack of data on MRI activity during the periods before and after treatments; and potential ascertainment bias due to different follow-up schedules between the AHSCT and DMTs group.

Albeit providing valuable information, the results shown in retrospective studies should plausibly be considered as a lower-bound for the true effectiveness of AHSCT, mostly due to a selection bias for more aggressive disease course in AHSCT-treated patients that cannot truly be eliminated in this setting.

Comparative evidence on the effect of AHSCT and HE-DMTs on PIRA is not available, though some hints on this issue may be inferred from the literature. PIRA was reported in 24% of 184 pw RRMS treated with natalizumab for a median of 5 years, and disease duration was the main factor for this event (Graf et al., 2021). In a pooled analysis from the OPERA trials, 14.4% of patients with relapsing MS treated with ocrelizumab showed 24-week confirmed PIRA at 96 weeks of follow-up (Kappos et al., 2020). The proportion of patients with PIRA was not provided in AHSCT studies, but, as some residual relapse activity was observed after AHSCT, EDSS worsening after transplant would encompass both PIRA and relapse-associated worsening (RAW). For example, rates of disability progression after cyclophosphamide-based AHSCT were 9.7% at 5 years in the MIST trial (Burt et al., 2019) and 5% at 4 years in 414 RRMS patients reported in a retrospective study (Burt et al., 2022), being cumulative proportion of cases with relapses 15.4% and 15%, respectively. In a cohort study including cases mostly treated with the BEAM+ATG protocol, disability worsening in RRMS was, in the proportion of cases, 14.5% at year 5 and, with relapses 21.9%, at the same timepoint (Boffa et al., 2021). Taking into account the known caveats of indirect comparisons, if rates of disability worsening after AHSCT were assumed (with plausible overestimation) as PIRA, these would appear still lower than those reported in RRMS patients treated with HE-DMTs. Even if rates were similar between HE-DMTs and AHSCT, this could still favour AHSCT, as patients who are initiated early on HE-DMTs to treat an aggressive clinical phenotype showed a higher risk of early PIRA in one study (Graf et al., 2021), and as AHSCT-treated patients are usually selected for aggressive disease course despite treatment with DMTs.

In conclusion, AHSCT is plausibly the treatment with the highest anti-inflammatory effect among available therapies (Burt et al., 2019; Sormani et al., 2017a), it has the unique potential of restoring immune tolerance, and CNS-penetrating protocols may act on compartmentalized inflammation (Cencioni et al., 2021). The radical suppression of inflammation and autoimmunity in early MS, potentially prior to the establishment of drivers of irreversible disability accrual, may dramatically reduce the risk of long-term disability progression and, possibly, the conversion to SPMS. Supporting this hypothesis, in a multicentre cohort of 281 pwMS affected by either progressive or relapsing MS, older age at AHSCT (HR 1.03, 95%CI 1.00–1.05) and a higher number of previous DMTs (HR 1.65, 95%CI 1.10–2.47) independently predicted disability accrual after transplant (Muraro et al., 2017b). The association between the number of DMTs received and disability worsening in RRMS was also confirmed in a multicentre cohort study, with HR of 1.57 (95%CI 1.12–2.20) (Boffa et al., 2021).

Comparative evidence on AHSCT and HE-DMTs, including

alemtuzumab, anti CD-20 monoclonal antibodies, natalizumab, and cladribine, is awaited from four ongoing RCTs: Star-MS, RAM-MS (clinicaltrials.gov 2023b), NET-MS, and BEAT-MS (clinicaltrials.gov 2023a).

3. Selection criteria: when could AHSCT be considered as a first-line treatment?

The improvement of the safety profile of AHSCT over time (Muraro et al., 2017a; Snowden et al., 2017) allows its use in less advanced MS compared to early studies, when it was essentially adopted as a "rescue therapy" in severe and highly disabled pwMS, who essentially did not have any remaining treatment options. However, due to short-term adverse events that are still higher compared with DMTs, careful patient selection is required to maximize the risk-benefit profile of the procedure. Provided that subjects with any medical comorbidity that may increase the risks of treatment are excluded, it would be reasonable to consider offering early AHSCT in pwMS affected by "aggressive/-malignant" disease, or in those who, although not fulfilling these definitions, are considered at high risk of unfavourable outcome.

3.1. *"Malignant/aggressive MS" and "highly active MS": current definitions*

"Malignant MS" was previously defined as a "disease with a rapid progressive course, leading to significant disability in multiple neurological systems or death in a relatively short time after disease onset" (Lublin and Reingold, 1996). The use of AHSCT in patients affected by "malignant MS" was reported in early studies (Alix et al., 2013; Fagius et al., 2008; Kimiskidis et al., 2008; Mancardi et al., 2005), and almost all the patients described had failed DMTs available at that time, even if treatment failure was not included in the definition. Accordingly, the EBMT guidelines from 2012 considered pw "malignant (Marburg type) MS, who develop severe disability in the previous year" (Snowden et al., 2012) eligible for AHSCT (level II of evidence recommendation). However, more recently, the term "malignant MS" was replaced by "aggressive MS", as the term malignant was no longer recommended since the 2014 revision of the MS phenotypic classification, as it was considered potentially misleading and determined only retrospectively (Lublin et al., 2014).

The term "aggressive MS" aims to identify pwMS who have an increased risk of rapid accrual of disability, compared to the general population, and therefore those who warrant aggressive treatment (Rush et al., 2015). The use of AHSCT for the treatment of "aggressive (malignant) MS not previously treated with a full course of DMT as defined in Ref. Menon et al. (2013)" is first mentioned in the EBMT guidelines from 2019, for whom AHSCT is endorsed as a "clinical option", with a level of evidence grade II (Sharrack et al., 2019). As stated in the guidelines, this means that the results of small patient cohorts show efficacy and acceptable toxicity of HSCT in this setting, but confirmatory randomised studies are missing and heterogeneity across studies complicates the interpretation of these data; the existing data support that HSCT is a valuable option for individual patients after careful discussion of risks and benefits, but its value needs further evaluation (Sharrack et al., 2019).

In the paper by Menon et al. (2013)cited in the EBMT guidelines, three definitions of "aggressive MS" were provided: (i) confirmed Expanded Disability Status Scale (EDSS) $\geq$6 within 5 years of MS onset; (ii) confirmed EDSS $\geq$6 by age 40; and (ii) SPMS within 3 years of a relapsing-onset course (Menon et al., 2013). While undoubtedly identifying cases with poor prognosis, all these definitions require the achievement of the disability milestone EDSS 6.0 or conversion to SPMS within a short time since diagnosis, therefore identifying a patient population which is far from the profile of the "ideal candidate" for AHSCT (Muraro et al., 2017a). In this respect, the definition suggested by Rush et al. may allow earlier identification of "aggressive RRMS" patients, being at least one of the following required: (i) EDSS score of 4 within 5 years of disease onset, (ii) $\geq$2 relapses with incomplete resolution in the past year, (iii) >2 MRI studies showing new or enlarging T2 or gadolinium-enhancing lesions despite treatment, and (iv) no response to therapy with one or more DMTs for up to 1 year (Rush et al., 2015). However, the use of a single criterion would probably also include patients with a milder disease course, and the combination of at least two features might be preferable for selecting treatment-naïve patients eligible for AHSCT.

In the absence of a consensus definition, several attempts of identifying "aggressive MS" have been reported, but most of the suggested definitions require either a long retrospective observation period or the achievement of definite disability milestones, or both (Iacobaeus et al., 2020). As a consequence, pw "aggressive MS" could be mostly recognized only when irreversible disability accrual and treatment-resistant drivers of the disease have already been established. This issue could be overcome by the implementation of prospective definitions, capable of identifying, timely (i.e. before accrual of meaningful disability) and accurately, patients at risk of unfavourable outcomes unless aggressively treated. In this regard, one study attempted to define "aggressive onset MS" as the presence of either of the followings: (i) two or more relapses in the year after onset and two or more gadolinium-enhancing lesions on brain MRI scan; or (ii) one relapse if it results in sustained baseline EDSS score of 3 along with two or more gadolinium-enhancing lesions (Kaunzner et al., 2016). In this study, 7.4% of patients met the criteria, and 12.5% of those who were started on aggressive treatment as their initial therapy showed evidence of disease activity over follow-up. This latter subgroup could represent an optimal target for AHSCT as a first-line treatment, but validated prospective definitions capable of identifying such patient population are currently lacking.

Highly selected patients who do not fulfil proposed definitions of "aggressive MS", but who bear risk factors for unfavourable outcomes and who show highly active disease may also be considered for early treatment with AHSCT. A previous position paper suggested that patients eligible for a RCT on AHSCT should have failed conventional treatment and have "highly active MS", defined as follows: $\geq$1 severe relapse (delta EDSS $\geq$1 and Functional System Score of $\geq$2 in motor, cerebellar or brain stem deficit (or documented changes in neurological examination consistent with these magnitudes) and/or incomplete recovery from clinically significant relapses; and $\geq$1 gadolinium-positive (Gd+) lesion of diameter $\geq$ 3 mm or accumulation of $\geq$ 0.3 T2 lesions/month in two consecutive MRI 6–12 months apart (Saccardi et al., 2012).

3.2. *Implementation of risk factors for poor prognosis*

Several factors have been associated with poor prognosis, including clinical and demographic characteristics, MRI and serum/CSF biomarkers (Briggs et al., 2019; Iacobaeus et al., 2020; Leguy et al., 2021; Rotstein and Montalban, 2019). As reviewing this topic is beyond the aim of the present paper, this section will focus on the main factors that could aid the clinician in identifying pwMS who may be eligible for early treatment with AHSCT, i.e. those cases who are at high risk for poor prognosis, but who still have not developed severe disability. These variables may include male sex (Weinshenker et al., 1991), high frequency of relapses over the first years from diagnosis (Confavreux et al., 2003; Scalfari et al., 2010), and incomplete recovery from relapses (Scott and Schramke, 2010). Early involvement of motor or cerebellar functional systems, cognition or sphincteric functions (Deloire et al., 2010; Langer-Gould et al., 2006; Stewart et al., 2017; Zarei et al., 2003) may also be considered, although patients who have established disability in these functional systems are less likely to benefit from AHSCT. Older age at MS onset (Bergamaschi et al., 2001) and early achievement of EDSS milestones (Malpas et al., 2019) should be used with caution, as the first correlates with disability progression after AHSCT (Muraro et al., 2017b), whereas the latter may identify patients

with low chance of disability recovery, unless milestones corresponding to mild disability (e.g. up to 3.0) are adopted, or the accrual of disability had occurred in the recent past. MRI parameters such as high T2 lesion load (more than 20 lesions at disease onset), presence of multiple gadolinium-enhancing lesions, and spinal cord/infratentorial involvement (providing that the latter is not associated with moderate to severe disability) (Tiu et al., 2022) may be useful in this setting. We think that other MRI markers associated with aggressive disease like black holes, early atrophy in the brain, spinal cord, and cortical and deep grey matter should not be adopted as they select mostly patients with established and irreversible neuronal loss, who therefore might show treatment-resistant progression of disability. Serum biomarkers include several molecules, being serum neurofilament light-chains the most promising (Ferreira-Atuesta et al., 2021) although their utility in patient selection for AHSCT remains unexplored.

Scores combining high-impact risk factors for severe outcomes were also explored to predict the achievement of disability milestones or aggressive disease course (Bose et al., 2022; Gasperini et al., 2021). The implementation of similar tools may aid in selecting pwMS eligible for early treatment with AHSCT, even if the rarity of this population and potential biases in real-life studies (such as the use of DMTs) make it challenging to validate a score in the AHSCT setting. Registry studies enroling wide patient cohorts and correcting for potential confounders may add valuable information on this topic.

4. AHSCT in treatment-naïve MS: available evidence

No randomized studies comparing AHSCT with HE-DMTs in treatment-naïve pwMS are available to date. One retrospective uncontrolled study focusing on the use of AHSCT in this patient population included 20 (10 male; 10 female) patients who received transplants across five centres (Das et al., 2021). Cases were included after being considered by the treating clinicians as characterized by features in keeping with an aggressive clinical course with poor prognostic markers. No pre-defined definition of "aggressive MS" was used, but when assessed retrospectively 18/20 patients fulfilled the criteria for "aggressive MS" by Rush et al. (2015), whereas the remaining two subjects had multiple poor prognostic markers. The patient population showed multiple clinical and radiological features suggestive of poor prognosis, including the following: multiple clinical relapses (at least 3 in the prior year in 12/20 cases) with incomplete recovery in all the patients, high EDSS scores and numerous new, enlarging or gadolinium-enhancing MRI lesions on multiple occasions, particularly in the brainstem, cerebellum and spinal cord. The median age at diagnosis and interval between diagnosis and AHSCT were 28 (range 17–47) years and 5 (range 1–20) months, respectively; the median last EDSS score before transplant was 5 (range 1.5–9.5). After mobilisation with cyclophosphamide (Cy) 2–4 g/m^2, patients received different conditioning regimens, according to the local treatment practice: busulfan (Bu) + Cy 200 mg/Kg + anti-thymocyte globulin (ATG) and CD34+ cells selection ($n = 4$), or BEAM (carmustine, cytarabine, etoposide, melphalan) + ATG ($n = 4$), or Cy 200 mg/Kg + ATG ($n = 12$). Over a median follow-up period of 30 (range 12–118) months, none of the patients experienced confirmed disability progression, and disability improved in 95% of the cases, with a median improvement of 2.25 (range 0–6.5) EDSS points ($p < 0.001$). No relapses were observed, and after re-baselining of MRI outcomes to the scan taken at month six post-AHSCT (therefore excluding the early MRI activity observed in three cases), NEDA status was achieved in 100% of cases. Although it is not reported whether the baseline assessment of EDSS was performed under relapse in some cases (potentially affecting the remarkable disability improvement observed), in this patient population AHSCT proved to be highly effective in inducing long-term remission of the disease, with an acceptable safety profile (discussed below).

More recently, a monocentric case series reported six patients affected by severe disability (median EDSS: 6.5) and progressive MS who were treated with AHSCT due to rapidly evolving course and lack of access to HE-DMTs (Lachnit et al., 2023). AHSCT was performed after a median of 14 and 7 months from MS onset and diagnosis, respectively, utilizing either Cy + ATG (5 cases) or BEAM+ATG (one case) regimens. Over a median follow-up of 30 (4–45) months after AHSCT, 3 patients continued to progress and 3 showed a persistent EDSS improvement; two patients relapsed, and one patient showed new lesions at the brain MRI taken 3 months after AHSCT. In this case series, clinical outcomes were overall less encouraging than those reported by Das et al. but AHSCT still seemed effective in half of the treated cases, despite the inclusion of patients with (i) progressive disease course (PP in some cases), (ii) high baseline EDSS, and (iii) long time interval between MS onset and treatment with AHSCT (more than 2 and 4 years in two cases), during which patients accumulated disability without receiving any DMTs.

Few other reports include treatment-naïve pwMS (Kvistad et al., 2022; Samijn et al., 2006), or cases who had previously received only chronic corticosteroids (Chen et al., 2012; Fassas et al., 1997; Nash et al., 2003; Saccardi et al., 2006), the latter included in early studies when current DMTs were not available yet. However, the outcomes of naïve patients were not provided separately from the entire cohort.

5. Safety of AHSCT in treatment-naïve patients

Treatment-naïve pwMS are expected to be at lower risk for severe adverse events after AHSCT due to a trend for a younger age, lower disability and lack of potential carryover complications of previous DMTs (Muraro et al., 2017b; Sormani et al., 2017b).

Furthermore, HE-DMTs exert long-standing effects on the immune system that may affect the safety of AHSCT (Sellner and Rommer, 2020), even when the transplant is performed after a wash-out period. Supporting this hypothesis, within six months after AHSCT (BEAM + ATG protocol), a higher incidence of major infections requiring hospitalization was reported in a small cohort of 13 consecutive pwMS (11 RR-, 2 SP-) who had received natalizumab before transplant compared to pwMS with similar baseline characteristics and who were treated with injectable or oral DMTs (Mariottini et al., 2015). Opposite to this preliminary finding, a recent retrospective study on 104 RRMS patients showed no differences in early adverse events and treatment-related mortality (TRM) between patients who had received, in the six months before transplant, DMTs with a long-lasting effect on the immune system (including alemtuzumab, cladribine, and rituximab) compared to those who did not (Kvistad et al., 2022). However, as acknowledged by the Authors, the number of patients in each DMT group was small, and information on treatment duration and prior exposure (i.e. treatment received more than six months before the transplant) was not available. Indeed, no data about the incidence of viral reactivations (eg CMV and/or EBV) in the follow-up of the two groups were given, which is supposed to have an impact on the overall safety profile of the procedure (Mehra et al., 2019).

Other long-term complications, such as the impairment of fertility, secondary autoimmune diseases, and secondary neoplasms, may be affected by previous exposure to DMTs. As an example, a higher risk of secondary infertility was associated with previous pulsed Cy treatment (Massarotti et al., 2021), and previous exposure to DMTs such as alemtuzumab may affect the incidence of secondary autoimmunity, although the difference was not significant in one study (Kvistad et al., 2022). Finally, a potential additive effect on cancer risk of previous treatment with definite classes of DMTs cannot be excluded (Lebrun and Rocher, 2018).

Despite the small sample size, the heterogeneity of conditioning protocol used, and the lack of a control group treated with standard DMTs, the safety profile of AHSCT was overall acceptable in the 20 treatment-naïve patients described by Das et al. (2021): no grade 4 toxicities nor TRM were reported. Besides expected common toxicities, secondary autoimmune disorders (thyroiditis in all the cases) were

observed in four patients (20%) and no secondary malignancy was diagnosed. Two patients conceived healthy babies (one female and one male patient's partner at months 7 and 22 after AHSCT, respectively). Similarly, no grade 4 non haematological toxicities nor TRM were observed in the case series by Lachnit et al. (2023).

6. Indication for AHSCT in the treatment-naive: opportunities and challenges

The evolving therapeutic landscape in MS has affected the selection of patients eligible to AHSCT, as the approval of HE-DMTs has reduced the probability of treatment failure. Notwithstanding, a minor but not negligible proportion of pwMS show disease activity despite treatment with HE-DMTs (Arrambide et al., 2020) and may therefore be destined to disability, unless otherwise effectively treated. Such cases, that could be retrospectively defined as affected by "aggressive MS", would probably have benefited from early treatment with AHSCT, if properly and timely identified. In this patient population, AHSCT could offer substantial advantages over HE-DMTs in long-term outcomes thanks to its maximal anti-inflammatory activity and potential for the restoration of immune tolerance.

While there is a consensus on the need for an early referral for AHSCT in case of failure to HE-DMTs, the use of AHSCT as a first-line treatment is currently debated, and comparative evidence on this issue is lacking and difficult to obtain (Das et al., 2021).

In our opinion, the current therapeutic scenario and the lack of validated strong predictors of unfavourable outcome only allows the use of AHSCT as a first-line treatment in highly selected cases, and the identification of such cases remains challenging. A possible suggestion would be to adopt the criterion selected by the European Medicine Agency (EMA) as therapeutic indication for natalizumab in treatment-naïve MS, i.e. "patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI" (Agency, 2023). However, it could be argued that the differences in safety profile between AHSCT and approved HE-DMTs would require the identification of a subset of patients who not only fulfil this criterion but are also expected not to respond to HE-DMTs.

On the other hand, it may be reasonable to evaluate for AHSCT patients who fail moderate-efficacy DMTs and exhibit poor prognostic factors, without requiring further (or higher grade) treatment failure.

Finally, as recommended by the EBMT guidelines (Sharrack et al., 2019), pw "aggressive (malignant) MS not previously treated with a full course of DMT" should receive transplant in a specialist centre with major experience in HSCT and with appropriate infrastructure, as defined by the Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT) and the EBMT (JACIE) guidelines (Aljurf et al., 2021), after a comprehensive assessment aimed at excluding any potential co-morbidity as determined by validated transplant-related risk score, such as hematopoietic cell transplantation-specific comorbidity index (HCT-CI) (Sorror et al., 2009). In this setting, eligibility for AHSCT should be evaluated by a multi-disciplinary team with high expertise in transplant for MS, providing a careful and comprehensive assessment of the benefit/risk ratio of the procedure. In the case of treatment-naïve patients, in addition to a rigorous medical evaluation, special attention should be given to the evaluation of cognitive functions and socio-cultural background to ensure a full understanding of the risks and benefits of transplant and all other available treatment options.

7. Conclusions

The improvement of the safety profile of AHSCT in MS has already allowed increasing anticipation of its use in recent years compared to older studies, which included mostly patients with advanced disease and reported poor outcomes. Nonetheless, prior failure of available DMTs remains a requirement for eligibility for AHSCT in most protocols, possibly resulting in a late referral of patients who have failed multiple treatments and who have acquired a burden of CNS pathology and clinical disability in the meantime. To optimally treat patients with highly active disease, AHSCT has recently been explored as a first-line treatment. One multicentric study focusing on this issue, including 20 naïve pwMS treated with different conditioning protocols, showed excellent neurological outcomes with good safety profile. However, the use of AHSCT in this setting is limited by safety concerns, and its role as a first-line treatment in "aggressive MS" remains highly controversial.

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