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REVIEW ARTICLE

Autologous hematopoietic stem cell transplantation in multiple sclerosis: 20 years of experience

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Abstract Intense immunosuppression followed by autologous hematopoietic stem cell transplantation (AHSCT) has been widely used in the last 20 years for the treatment of aggressive forms of autoimmune disorders, especially multiple sclerosis (MS). All clinical studies, although small and uncontrolled, demonstrate a great efficacy of this procedure in halting inflammation and disease activity, even in those patients affected by "malignant forms" of MS. The long-term follow-up has also revealed the possible maintenance of positive results in the course of time, and this evidence is supported by immunological data that suggest the possibility of a resetting of the immune system after AHSCT. The safety of AHSCT has improved in the last years, but the transplant related mortality is still nowadays of about 1-2 %, pointing out that a careful selection of patients to submit to AHSCT is mandatory. The long clinical experience allowed to identify the ideal candidate: a young patient, with a short disease duration, with recurring and disabling relapses and the presence of inflammatory activity on brain magnetic resonance scans, unresponsive to approved therapies. A large, randomized clinical study comparing AHSCT with the best approved therapies is still necessary to confirm the role of transplantation in MS treatment.

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Introduction

In the last 20 years, intense immunosuppression followed by autologous hematopoietic stem cell transplantation (AHSCT) has been utilized as a treatment option for aggressive forms of autoimmune diseases, such as erythematous systemic lupus, rheumatoid arthritis (RA) and, among neurological diseases, multiple sclerosis (MS). Traditionally, HSCT is being used for the treatment of hematological tumors with the aim of destroying the malignant immune system with a high-dose chemotherapy, followed by autologous or allogeneic stem cell transplantation to reconstitute the immune system. In allogenic transplantation, donor and recipient are immunologically distinct, and the transplanted stem cells, which come from a healthy donor, can give rise to a new immune system and possibly eliminate residual cancer cells, survived to conditioning regimen (graft versus tumor, GVT). The counterpart of this beneficial effect is the graft versus host disease (GvHD), when the newly transplanted cells attack the recipient's cells, recognized as foreign; this reaction can lead the patient to important complications and also to death. In autologous transplantation, the mortality risk is by far lower because of the absence of GvHD. Following this rationale, AHSCT has been considered for the treatment of severe autoimmune diseases characterized by an abnormal lymphohematopoietic system, albeit non-malignant, with the aim to eradicate self-reactive cells and to reconstitute a renewed immune system.

Animal studies

The treatment of relapsing experimental autoimmune encephalomyelitis (EAE) of rats, an animal model of MS, with total body irradiation (TBI) or cyclophosphamide (CY) and busulfan (Bu) followed by allogeneic bone marrow transplantation (BMT), can induce a complete remission of disease and prevent spontaneous and induced (after reimmunization) relapses [1]. Good results have also been obtained with syngeneic and pseudoautologous BMT demonstrating an accelerated recovery from paresis in treated animals compared with placebo, with a relapse rate, however, of about 6–33 % [2]. This higher relapse rate is considered to be related to the presence of surviving lymphocytes in the transferred autologous bone marrow [3]. Considering the higher mortality risk of allogeneic transplantation and the efficacy of pseudoautologous BMT in EAE, the second approach has been proposed for the treatment of severe forms of autoimmune disorders and, therefore, also of MS.

The first group of 15 patients, with advanced and active disease, was treated since April 1995 in Greece by Fassas and colleagues [4]: this first pilot study, even with the limitations due to the very short follow-up, demonstrated that AHSCT was feasible in MS patients, offering some evidences of clinical benefits. Since then, numerous patients affected with aggressive forms of MS have been treated worldwide in the context of small phase I/II studies using different inclusion criteria and different combinations of drugs for mobilization and conditioning regimen (see Table 1).

Transplant procedures

The mobilization of HSCs from peripheral blood is usually performed with cyclophosphamide (CY, 2–4 g/m^2 total dose in 1 or 2 days) followed by granulocyte colony-stimulating factor (G-CSF) from 5 to 10 mcg/kg daily until the end of mobilization or with G-CSF alone (5–16 mcg/kg daily). The use of G-CSF alone is frequently associated with flare of disease activity, therefore, the association with CY is preferable, also considering the beneficial effect of this high dose of CY on active inflammation and, consequently, on neurological symptoms and the ability to reduce the number of autoreactive T cells in the graft [5, 6]. When G-CSF is used alone, steroids (usually prednisone 1 mg/kg) can be administered for at least 1 week to prevent disease reactivation, related to massive release of cytokines [7].

Since there is a significant correlation between infused CD34+ cells dose and time to engraftment, a number of 3×10^6 CD34+ cells/kg of body weight is the minimum dose considered safe for the patient [8]. The graft collected through leukapheresis can be manipulated for the ex vivo selection of CD34+ cells to purify the graft from autoreactive T cells that can be responsible for the reappearance of MS symptoms after HSCT [7, 9, 10]. A study evaluating AHSCT in RA has shown no differences of outcomes among patients receiving unmanipulated cells and those receiving CD34-selected cells; therefore, the use of unmanipulated graft is commonly preferred, avoiding an additional cost in the procedure [11]. The graft is cryopreserved for about 40–60 days, when the patient is admitted to the hospital to undergo intense immunosuppression with the aim of destroying the autoreactive immune system. Different associations of drugs have been utilized to perform conditioning regimen, but no consensus have been reached to identify a "gold standard." The conditioning regimen can be classified as high-, intermediate-, and low-intensity regimens. High-intensity regimens include total body irradiation (TBI) 1200 cGy plus CY 120 mg/kg total dose in 2 days [10], TBI 800–1000 cGy plus CY 120 mg/kg total dose in 2 days, and antithymocyte globulin (ATG) 15 mg/kg for 5–6 days [7, 12], busulfan (1 mg/kg in 16 doses) plus CY (120 mg/kg) and ATG 10 mg/kg for 3 days [13], busulfan (16 mg/kg) plus CY (200 mg/kg) [14], or busulfan alone (16 mg/kg) [15]. These high-intensity regimens in animal studies seem to be associated with a better clinical outcome, but in humans, they have a higher toxicity and are associated with a higher transplant-related mortality (TRM) [16, 17]. The most widely diffused scheme, at least in Europe, is BEAM, an intermediate-intensity regimen, which includes 300 mg/m^2 carmustine (BCNU) at day −6, 200 mg/m^2 etoposide and 200 mg/m^2 cytarabine (AraC) from day −5 to day −2, and 140 mg/m^2 melphalan at day −1, usually followed by ATG at a total dose of 7.5–10 mg/kg at day +1 and +2 [15, 18–25]. Other intermediate-intensity protocols consist of BNCU 300 mg/m^2 plus CY 150 mg/kg total dose in 3 days and ATG 15 mg/kg [26], mini BEAM with low dose of the same drugs provided for BEAM (BCNU 300 mg/m^2, etoposide 75–100 mg/m^2, AraC 75–100 mg/m^2 and melphalan 50–100 mg/m^2), or BNCU 300 mg/m^2 plus melphalan 50–100 mg/m^2 [27]. Low-intensity regimens have been proposed to reduce the toxicity related to intense immunosuppression, using a lymphoablative approach, instead of a myeloablative approach. CY 120–200 mg/kg and alemtuzumab 20 mg or ATG 1–5 mg/kg daily [19, 28, 29] have been used; the administration of alemtuzumab has been replaced by ATG for the occurrence of two cases of immune thrombocytopenic purpura, requiring treatment with rituximab and CY [28]. The low-intensity therapy is not able to effectively control long-term inflammation and disease activity, at least in our experience [29]. An intermediate-intensity regimen, like BEAM, can be considered

Table 1 Studies about AHSCT in MS

	Patients (*n*)	EDSS	Mobilization	Conditioning regimen	Outcome		Death
					FU	PFS (%)	
Kozak et al. [54]	33	5.0–8.0	Cy + G-CSF	BEAM + ATG or CD34 selection	5	70	0
Openshaw et al. [13]	5	5.5–7.5	G-CSF	Busulfano + Cy + ATG + CD34 selection	1.8	40	1
Nash et al. [7]	26	5.0–8.0	G-CSF	TBI + Cy + ATG + CD34 selection	3	73	1
Burt et al. [10]	21	3.0–8.0	G-CSF or CY + G-CSF	TBI + Cy	1.8	61	0
Ni et al. [55]	21	5.0–9.5	Cy + G-CSF	BEAM + ATG + CD34 selection or TBI + Cy + ATG + CD34 selection	3.5	75	2
Xu et al. [23]	22	4.5–7.5	G-CSF	BEAM + CD34 selection	5	77	0
Samijn et al. [12]	14	5.5–6.5	BOM	TBI + Cy + ATG	3	36	0
Freedman et al. [14]	17	3.0–6.0	Cy + G-CSF	Busulfano + Cy	3	75	0
Shevchenko et al. [22]	45	1.5–8.0	Cy + G-CSF	BEAM + ATG	6	72	0
Saiz et al. [26]	14	4.5–6.5	Cy + G-CSF	BNCU + Cy + ATG + CD34 selection	6	62.5	0
Burt et al. [28]	21	2.0–5.5	Cy + G-CSF	Cy + alemtuzumab or Cy + ATG	3	100	0
Hamerschlack et al. [19]	41	3.0–6.5	Cy + G-CSF	BEAM + ATG or Cy + ATG	2.5	58.5 (EFS)	3
Krasulova et al. [21]	26	2.5–7.5	Cy + G-CSF	BEAM + ATG or BEAM + CD34 selection or BEAM + ATG + CD34 selection	6	29.2	0
Fassas et al. [15]	35	4.5–8.0	Cy + G-CSF	BEAM + CD34 selection or BEAM + ATG o Busulfano	15	25	2
Shevchenko et al. [27]	95	1.5–8.0	G-CSF	BM o miniBEAM +/− ATG	5	82	0
Mancardi et al. [24]	74	3.5–9	Cy + G-CSF	BEAM + ATG	5	66	2
Chen et al. [18]	25	3.0–9.5	Cy + G-CSF	BEAM + ATG + CD34 selection	9	48	2
Bowen et al. [56]	26	5.0–8.0	G-CSF	TBI + Cy + ATG + CD34 selection	6	44	1
Burman et al. [20]	48	1.0–8.5	Cy + G-CSF	BEAM + ATG or Cy + ATG	5	77	0
Nash et al. [25]	25	3.0–5.5	G-CSF	BEAM + ATG + CD34 selection	3	91	0
Burt et al. [33]	145	2.0–6.0	Cy + G-CSF	Cy + alemtuzumab or Cy + ATG	4	87	0
Schevchenko et al. [32]	99	1.5–8.0	G-CSF	BM or miniBEAM +/− ATG	8	83	0

PFS progression free survival, EFS event free survival

the protocol of choice in the light of its positive clinical and radiological outcomes along with a satisfactory toxicity profile.

Clinical outcomes

All published clinical phase I/II studies agree with the ability of AHSCT to achieve stabilization, and in some cases, an improvement of disease, at least in the mid-term, in patients affected by aggressive forms of MS unresponsive to traditional therapies. The retrospective analysis of the European Group for Blood and Marrow Transplantation (EBMT), which include the largest cohort of patients, of 2001, 2006, and 2010 [17, 30, 31], shows a progression free survival (PFS) at 3 and 5 years of 74 and 45 %, respectively. Table 1 summarizes the clinical results of all principal studies on AHSCT in MS. The PFS at 3 years range from 36 % of Samjin et al. [12] to 91 % of Nash et al. [25]. Shevchenko and colleagues [32] treated in

Russia a large group of patients (99) with a reduced-intensity regimen based on BEAM showing a PFS at 8 years of 83 %. Other studies with a long follow-up (FU) maintain encouraging results with a PFS of 66 % at 5 years in the Italian group [24], of 77 % at 5 years in the Swedish study [20] and of 25 % at 15 years for Fassas et al. [15]. Most studies demonstrate that after AHSCT, there is not only an arrest in disease progression, but also an improvement of disability with reduction of EDSS scores. Shevchenko reported in 30 out of 64 patients (47 %) a reduction of at least 0.5 point on EDSS at a 3-year FU [32], similar findings with a mean improvement of 0.5 point on EDSS at 3 years FU were reported by Nash et al. [25]. In the study of Burt et al. [33, 34], a decrease of more than 1 point on EDSS was demonstrated in 50 and 64 % of patients at 2 and 4 years from transplantation and the median EDSS score improved from 4 at baseline, to 3 at 2 years FU and 2.5 at 4 years FU. In some patients, this EDSS improvement can be maintained over time as demonstrated by the Italian study [24] with 27 % of patients showing an EDSS improvement confirmed at long-term FU between 7 and 12 years and by the Greek study [15] with two patients showing stabilized improvement at 7 and 8 years FU. These results, even if in a small percentage of patients, remain very interesting, considering that all patients treated with AHSCT were affected by aggressive and rapidly progressive forms of MS. A few studies evaluated the effect of AHSCT on a functional score showing an improvement in all Multiple Sclerosis Functional Composite (MSFC) domains [25, 33]. Remarkable results have also been obtained in terms of control of clinical relapses. It is of main relevance to underline that in the first studies, was enrolled a population of severe disabled MS patients, usually in the progressive phase of the disease, while in the more recent experience, MS cases still in the relapsing–remitting (RR) phase of the disease were recruited, improving, therefore, the final clinical outcome of the treated patients. There is a general agreement that AHSCT has a striking effect on disease activity and, consequently, on relapse rate. In the Russian group, 40 RRMS patients were included and 39 were relapse-free at 3 years FU [27], Mancardi et al. [24] described a percentage of relapse-free patients of 85 % at 5 years FU, and Nash et al. [25] described a percentage of 86 % at 3 years FU; in the group of patients treated by Krasulova [21], the annualized relapse rate (ARR) drops from 2 in the year before AHSCT to 0 within the first 2 years after AHSCT. It was also demonstrated that the clinical outcome of AHSCT is influenced by the previous clinical course of disease, as PFS is higher, with variable degree of statistical significance, in RRMS vs SPMS. In the study by Krasulova [21], PFS at 3 years FU was 84.4 % in RRMS and 60 % in SPMS and in the Italian study [24] PFS at 5 years was 71 % in RRMS vs 62 % in SPMS. The variable most significantly related to a better clinical outcome is the detection of disease activity demonstrated by the presence of gadolinium (Gd) enhancing lesions on magnetic resonance imaging (MRI) scans: the PFS in Gd+ patients was 87 % at 5 years FU vs 46 % in Gd− patients in the Italian group [24], confirmed by the long-term FU results of Fassas et al. [15] with a PFS of 44 % at 15 years FU in Gd+ patients vs 10 % in Gd−. Age and disease duration have also a positive correlation with clinical results: a better clinical outcome is demonstrated in younger patient (age <40 years) with shorter disease duration (<5 years) [17, 21]. AHSCT is also effective in the treatment of malignant forms of MS, classified as aggressive forms that can lead rapidly to a high burden of disability and, at times, even to death [35] in a short period of time. Some case reports demonstrate that AHSCT can halt, even after failure of immunosuppressive and immunomodulatory drugs, disease progression, allowing not only stabilization, but also an improvement of disability [36–38]. A few studies evaluated patients' feelings about physical and psychological changes in their lives related to AHSCT using self-assessment questionnaires like Multiple Sclerosis Quality of Life-54 (MSQoL-54) or Medical Outcomes Study 36-Item Short-Form Health Survey (MOS SF-36), revealing an improvement in quality of life after transplantation [39, 40]. In particular, in the Russian study [32], QoL evaluation was performed in 61 patients: at 12 months post-transplantation, a statistically significant increase in all SF-36 scales, except two items, was registered as compared with baseline, confirming the positive effect of AHSCT on perceived QoL.

MRI outcomes

AHSCT has a striking effect in reducing and also extinguishing inflammatory activity detected at brain MRI. All studies show a disappearance or a marked reduction of Gd-enhancing lesions after AHSCT that lasts over time, with a few cases of disease reactivation. Ten patients in the Italian study [41] underwent serial brain MRI before transplantation, monthly for the subsequent 6 months and then every 3 months for 2 years with a triple dose of Gd to better reveal active lesions. In the 3 months before AHSCT, 341 Gd+ lesions were detected, while only five lesions were present in the 3 months after transplantation, and no more active lesions appeared in subsequent months until the end of FU. Burman et al. [20] demonstrated an MRI free survival at 5 years FU of 85 %. In the Chinese study [18], 58 % of patients (7/12) had active lesions at baseline and all turned to inactive status after AHSCT. This great efficacy in switching off inflammation has not been confirmed

in the small group of patients treated in Italy with a low-intensity regimen based on CY (120 mg/kg) plus ATG [29]. After an initial important reduction, even if not complete suppression, of disease activity, in six out of seven patients, inflammation detected at MRI reappeared and one patient showed a dramatic disease reactivation with 31 Gd-enhancing lesions at MRI scan 9 months after AHSCT. Better results have been obtained with a low-intensity regimen, but with a higher dose of CY (200 mg/kg), by Burt et al. [33]: the mean number of Gd+ lesions was 3.22 at 3–6 months before HSCT and dropped to 0.01 at 6 months, 0.13 at 1 year, 0.07 at 2 years, and 0.08 at 5 years after transplantation. These findings suggest that lymphoablative regimens are probably less efficacious than myeloablative regimen in suppressing disease activity. A few studies also evaluated the effect of AHSCT on T2 lesion load, demonstrating a reduction of T2 lesions volume (T2LV). Burt et al. [33] reported in 128 out of 145 transplanted patients, with a mean FU of 2 years, a reduction of median T2LV of 33 %; in 24 patients treated by Nash et al. [25], T2LV significantly decreased from baseline through 3 years FU. Despite this strong effect in reducing inflammation and the number of new or enlarging T2 lesions, data about the ability of AHSCT to slow down progression of brain atrophy are not clear. Two studies demonstrated a decrease in brain volume in the 2 years after transplantation that exceeded the previous reported values in MS patients [42, 43]. This reduction cannot be completely justified by the so-called "pseudoatrophy," the obvious tissue loss consequent to resolution of edema after suppression of inflammation, and it could be related to a possible toxic effect of drugs used for intense immunosuppression and to the neurodegenerative process that persists even if inflammation has been halted. Two studies [44, 45] evaluated brain MRI during a longer FU, demonstrating, however, that the rate of brain tissue loss is higher in the 2 years after transplantation, but decreases significantly in the third year, becoming similar or lower to reported values of brain atrophy in MS patients. These findings suggest the critical role of pseudoatrophy and pharmacological neurotoxicity in the first years after AHSCT and the possible role of reparative mechanisms in the subsequent years.

Safety profile

AHSCT is a very challenging procedure due to the high toxicity of drugs used for mobilization and conditioning regimen, with a not negligible mortality risk that, considering the percentage of TRM reported in different studies (see Table 1), can be nowadays probably estimated of about 1–2 %. The first EBMT analysis, evaluating patients treated from 1995 to 2000, showed a TRM of 7.3 %, while the TRM from 2001 to 2007 was of 1.3 %, showing a significant improvement in terms of safety [17]. This improvement is probably related to the exclusion of high-intensity approach with TBI and busulfan, to the better selection of patients and to the long experience of neurologist and hematologist. This improvement of safety is also confirmed by the absence of toxic-related death in recent studies involving a great number of patients, such as the Russian study [32] with 99 patients and the American study [33] with 145 patients, where the low-intensity regimen was utilized. Beyond TRM, the most common early (within 100 days from the procedure) adverse events related to AHSCT are neutropenic fever, experienced by at least 50 % of treated patients, infectious diseases, above all urinary tract and respiratory infections, complicated in about 10–30 % of cases with sepsis, liver toxicity, mucositis, diarrhea, and reactivation of varicella zoster virus. Among late adverse events (more than 100 days after transplantation), it is important to consider the occurrence of secondary autoimmune diseases (AD). Only few studies reported data about secondary autoimmunity: Samijn et al. [12], in a group of 14 patients, found two cases of autoimmune thyroiditis and one case with only positive serum antibodies (Ab) without clinical or laboratory signs of thyroid dysfunction; the EBMT analysis of 183 patients treated from 1995 showed the occurrence of new AD in five patients (3.4 %): three autoimmune thyroiditis and two acquired antifactor VIII inhibitors. In the Swedish cohort of patients [20], four (8.3 %) developed hypo- or hyperthyroidism, one developed Crohn's disease and one alopecia areata. In the recent study of Burt et al. [33], the incidence rate of posttransplant immune dysfunction was 22.7 % in patients receiving alemtuzumab (where, however, the occurrence of autoimmune disease is well known), compared with 6.9 % in patients receiving ATG [in particular, seven patients developed an immune-mediated thrombocytopenia (ITP) and seven a thyroid dysfunction]. The reported incidence of secondary immune dysfunctions in patients undergoing AHSCT for AD is around 9 % at 5 years FU along with data from EBMT [46]. Several mechanisms have been proposed to justify the occurrence of these complications, such as the loss of peripheral tolerance after conditioning regimen, the proliferation of autoreactive cells by homeostatic expansion, and the failure of negative selection during de novo thymic ontogenesis of T lymphocytes. These immunological interpretations may explain the fact that the more intense T cell depleting therapies are associated with an increased incidence of secondary AD after AHSCT. More studies are necessary to evaluate the actual risk of developing secondary AD in MS patients and to understand the underlying immunological modifications. The aggressive

chemotherapy is obviously related to a high risk of premature menopause and infertility; therefore, it is important to suggest a fertility counseling, at least when the clinical course of disease allows a little delay in the beginning of the procedure. The group of Burman et al. [20] reported data about pregnancy outcomes. Among 51 patients, eight pregnancies in four women occurred with five healthy infants (including a pair of twins), two spontaneous abortions, one ectopic pregnancy, and one legal abortion. Moreover, two infants were born from in vitro fertilization. A recent analysis from EBMT [47] reports in seven MS female patients 11 pregnancies: seven healthy life births, two natural abortions, and two induced abortions.

Immunological considerations

The long-term immunologic reconstitution after AHSCT is usually characterized by a slow increase in CD19+ B lymphocytes that reach a normal value at 6 months, while CD3–CD56+ NK cells are in the normal range, since 3 months after AHSCT. CD8+ T lymphocytes reach normal values 3 months after transplantation and remain stable, while CD4+ cells remain under normal value until 12 months with a consequently sustained inversion of CD4/CD8 ratio [48]. The analysis of lymphocyte subsets showed that in the initial immunologic reconstitution, there was a prevalence of memory cells resulting from homeostatic proliferation in a lymphopenic environment, until month 6. Then, the number of these central-memory CD4+ cells (CD45RA−/CD45RO+/CD27+) decreased, and at 2 years after transplantation, the total number of memory cells was reduced as compared with baseline. On the contrary, CD4+ naïve T lymphocytes (CD45RA+/CD45RO−/CD27+), initially reduced at 6 months post AHSCT, at 2 years had almost doubled. Moreover, the analysis of T cell receptor repertoire showed the reconstitution of an overall broader clonal diversity and an extensive renewal of clonal specificities, demonstrating an important immune regeneration, probably related to the long-term control of disease activity [49]. In a little group of 23 patients, the TCR diversity was higher in 19 patients having a complete response compared with those (4) failing to meet the primary endpoint [50]. In a group of 14 patients, the analysis of cytokine profiles showed, at 12 months post-treatment, an essentially identical Th1 and Th2 response after treatment in all patients, while there was a significant decrease in Th17 cells, producing IL-17, a cytokine directly involved in disruption of blood–brain barrier (BBB) and CD4 lymphocytes recruitment [51]. Even after a treatment with a non-myeloablative conditioning regimen, significant changes have been demonstrated in the immune regeneration. At 6 months post-AHSCT, there was an important, although transient, increase in CD4+ FoxP3+ T cells and $CD56^{high}$ NK cells with immunoregolatory function, with a possible role in modulation of activated effector cells during early antigen reexperiencing. It was also evidenced a radical depletion, during a 2 years FU period, of $CD161^{high}$ CD8+ T cells, producing proinflammatory cytokines as INFγ, TNFα, and IL17 [52]. These findings suggest that the beneficial effect of AHSCT is not only related to the intense immunosuppression with a massive destruction of autoreactive cells, but also to an important regeneration and renewal of the immune system, probably responsible of the long-term positive effect of AHSCT on disease course.

The phase II study: ASTIMS

Recently, the results of the first study comparing Mitoxantrone (MTX) versus AHSCT for the treatment of aggressive forms of MS have been published. This study was originally conceived as a phase III study with the aim to evaluate the possible clinical superiority of AHSCT compared with approved therapies for the treatment of rapidly progressive forms of MS. Due to the difficulties of enrollment, the primary endpoint was modified, and the study became a phase II study, evaluating disease activity measured by the cumulative number of new T2 lesions. The relapse rate was reduced in patients treated with AHSCT compared with MTX. During a 4-year FU, AHSCT significantly reduced by 79 % the number of new T2 lesions compared with MTX (median number 2.5 vs 8). No new Gd-enhancing lesions appeared on brain MRI in the AHSCT group, while 56 % of patients treated with MTX presented at least 1 active lesion. These data strongly confirm the great activity of AHSCT on MRI and relapse rate, by far better than a strong immunosuppressant like MTX [53]. No difference was, however, observed in the disability progression between the small two groups of patients.

Final considerations

All published data, even if obtained from different trials, with a limited number of patients, using distinct inclusion and exclusion criteria, dissimilar type of patients and various kind of mobilization and conditioning regimens, demonstrate a great efficacy of AHSCT in the treatment of aggressive forms of MS unresponsive to therapeutic attempts with approved or off-label drugs and confirm that AHSCT is probably the best chance for patients presenting a malignant form of disease with a severe disease course. Undoubtedly, the procedure has a not negligible mortality

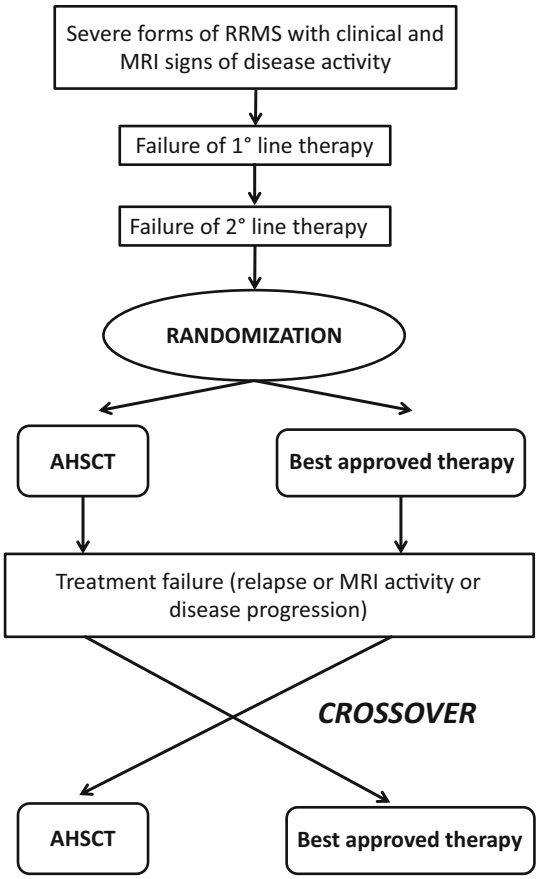

Fig. 1 Trial design (adapted from Saccardi et al. MSJ 2012)

risk that has to be considered in the treatment of a disease, like MS, that, usually, is not life threatening. In the last decade, thanks to the gained experience of neurologists and hematologists, the procedure related side effects and the mortality risk are decreased, but it is still around 1–2 % of treated cases. The ideal candidate to transplantation, that is to say the patient that can take the greater advantage from the procedure with the smaller amount of risks, is a young patient (<40 years old) with a short disease duration (<5 years) who experiences recurrent relapses with active inflammation demonstrated at brain MRI, despite immunomodulatory and immunosuppressive therapies. At the moment, there are therapies that are highly effective in MS, such as natalizumab and alemtuzumab. Both the drugs, however, carry serious problems, progressive multifocal leukoencephalopathy for natalizumab and a high probability to acquire an autoimmune disease that in some cases, such as immune thrombocytopenic purpura and antiglomerular basement membrane disease, can be serious. Ocrelizumab, that will be available in the next future, is a new very promising medication, but its side effects, at least in the long-term, are unknown, even if the safety profile in the short period is similar to the already approved drugs. There is, therefore, the need to clarify the right place of AHSCT in the therapeutic strategy for severe forms of MS. Therefore, considering all positive data previously discussed and the current large knowledge about AHSCT, it is necessary to organize a phase III clinical trial, comparing AHSCT with the best present approved therapy. A possible perspective randomized controlled trial of AHSCT for aggressive forms of MS has been already outlined [57]. In the design of this study, slightly modified in the present review, patients that failed first- and second-line therapies, still in the RR phase of the disease, with clinical and MRI signs of disease activity, will be randomized in the AHSCT or in the best approved therapy arm according to the judgment of the treating neurologist. Treatment failure will be the primary outcome, defined as the occurrence of a severe relapse or sustained EDSS worsening or a new Gd+ or T2 lesion at MRI. If the patient reaches the endpoint, he has the option to cross over and receive the treatment of the other arm (Fig. 1). Even if the neurologist with experience in AHSCT knows its profound efficacy, it appears to be mandatory to organize an international study with the aim to clarify the correct position of AHSCT in the therapeutic armamentarium of severe forms of MS.

Compliance with ethical standards

Conflicts of interest D.C has no conflict of interest. G.M has received honoraria for lecturing, travel expenses for attending meetings, and financial support for research form Bayer Schering, Biogen Idec, Sanofi Aventis, Teva, Genzyme and Merck Serono Pharmaceuticals.

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