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ORIGINAL ARTICLE

Long-term outcomes of autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis: physician's and patient's perspectives

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Abstract High-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (AHSCT) is a promising approach to treatment of multiple sclerosis (MS) patients. In this paper, we present the long-term outcomes of a prospective single-center study with the analysis of the safety and efficacy of HDIT + AHSCT with reduced-intensity BEAM-like conditioning regimen in 99 MS patients: mean age—35 years old; male/female—39/60; median Expanded Disability Status Scale (EDSS) = 3.5; 43 relapsing/remitting MS, 56 progressive MS. No transplant-related deaths were observed. The mobilization and transplantation procedures were well tolerated. At 6 months post-transplant, neurological improvement or stabilization was observed in all the patients except one. Cumulative incidence of disease progression was 16.7 % at 8 years after HDIT + AHSCT. Estimated event-free survival at median follow-up of 48.9 months was 80 %: 83.3 % in relapsing/remitting MS vs 75.5 % in progressive MS. Sixty-four patients who did not progress during the first 3 years post-transplant and were monitored for more than 3 years were included in long-term outcome analysis. At the median long-term follow-up of 62 months, 47 % of patients improved by at least 0.5 points on the EDSS scale as compared to baseline and exhibited improvement during the entire period of follow-up; 45 % of patients were stable. No active, new, or enlarging lesions on magnetic resonance imaging were registered in patients without disease progression. AHSCT was accompanied by a significant improvement in patient's quality of life. Due to the fact that patient selection was quite different to the other studies and that the information about disease activity prior in the disease course and its treatment was inhomogeneous, comparison with the results in the literature should be done with caution. Thus, the risk/benefit ratio of HDIT + AHSCT with reduced-intensity BEAM-like conditioning regimen in our population of MS patients is very favorable. The consistency of our long-term clinical and quality of life results, together with the persistence of improvement, is in favor of the efficacy and safety of this treatment approach in MS patients.

Keywords Autologous hematopoietic stem cell transplantation · Clinical outcomes · Multiple sclerosis · Patient-reported outcomes · Long-term outcomes

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) caused by autoimmune reactivity of T cells towards CNS myelin components. Ten years after onset, about 50 % of patients have a chronic progressive

course [1, 2] with this proportion increasing to 70 % after 15 years from disease onset and to 85 % after 25 years [3]. Inflammation of the CNS is a prominent feature of MS. Though the role of inflammation has most often been studied in the relapsing/remitting MS (RRMS), it is present and also likely plays a role in the progressive forms (PrMS) [4]. MS is one of the most common neurological disorders, which mainly affects young adults, and causes gradual decrease of their quality of life (QoL). Medications currently approved for MS treatment are only partially effective for slowing progression or reducing the number of relapses and not effective for progressive MS.

High-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (AHSCT) was proposed as a new and promising therapy for MS patients [5–7]. The rationale for this method is that ablation of the aberrant immune system followed by reconstitution of the new immune system from hematopoietic stem cells may alter the characteristics of the T cell responses and other immunological properties which may improve the clinical course of MS. Since 1995, centers in Europe, North and South America, Russia, China, Israel, and Australia have the experience of using HDIT + AHSCT for MS treatment. At present, BEAM as the conditioning regimen is most frequently used. BEAM is an intermediate-intensity conditioning regimen, pioneered by Fassas et al. [6]. Several clinical studies have addressed the issue of safety and efficacy of AHSCT with BEAM as conditioning regimen in MS and a certain clinical benefit has been shown [6, 8–14]. Recently, it was shown that the low-intensity regimen, namely the cyclophosphamide (CY)/rabbit anti-thymocyte globulin (ATG) regimen, is associated with similar outcome results, but presented less toxicity when compared with the BEAM/horse ATG regimen [15]. The use of less-intensive conditioning regimens is supported by the suggestion that AHSCT is not only an immunosuppressive therapy but also could have an immunomodulatory component [16]. Taking into account that a moderate intensity and less toxic regimen could induce durable long-term remission, comparable with the high-intensity regimens, but without being associated with the higher transplant-related mortality characteristic of high-intensity regimens, we aimed to study if the reduced-intensity regimens based on BEAM are safe and effective in MS patients. Our initial findings with the use of HDIT + AHSCT with the reduced-intensity conditioning regimen have been published previously [12, 17]. To prove the effect of HDIT + AHSCT with the reduced-intensity regimen, information about long-term outcomes is worthwhile. In addition, comprehensive evaluation of treatment outcomes after HDIT + AHSCT is of great importance. For MS patients, both disease-free period and improvement of patient's QoL are recognized as important outcome parameters.

In this paper, we report the long-term outcomes of HDIT + AHSCT with reduced-intensity regimen based on BEAM in MS patients with various types of disease. In this study, we aimed to evaluate both clinical and patient-reported outcomes at long-term follow-up after HDIT + AHSCT. Separate analysis in patients with relapsing-remitting MS and in patients with progressive course of the disease was performed.

Patients and methods

Ninety-nine patients were treated with HDIT + AHSCT in the Transplantation Unit, Department of Hematology and Cellular Therapy, National Medical Surgical Center in Moscow, from October 2005 to July 2011. The study was conducted according to the principles of the Helsinki Declaration and was approved by the Institute Review Board and local Ethics Committee before initiation. The patients enrolled in the study previously have been treated in different centers; in a number of cases, information about disease activity prior in the disease course and its treatment was scarce. All patients gave written informed consent. Patients were eligible if they were aged between 18 and 55 years and met the McDonald criteria for clinically definite MS [18]. Other criteria for patient selection were as follows: Expanded Disability Status Scale (EDSS) score 1.5–8.0, normal mental status, absence of severe concomitant diseases, +/− gadolinium-enhancing lesions, and no treatment with interferons or immunosuppressive agents within 3 months before enrollment. The vast majority of patients included in the study failed to conventional therapy including beta-interferon, copaxone, chemotherapy, and steroids. There were 43 RRMS, 35 secondary progressive MS (SPMS), 18 primary progressive MS (PPMS), and 3 progressive relapsing (PRMS) patients. Male/female ratio was 39/60. Age at the time of AHSCT was 18–54 years (mean 34.6). Median EDSS prior to transplantation was 3.5 (range 1.5–8.5). One patient who was enrolled in the study with EDSS 8.0 worsened by the time of transplantation to EDSS 8.5. According to pre-transplant magnetic resonance imaging (MRI) scans, 40 % patients exhibited gadolinium-enhancing lesions; others were without. MS duration was from 0.5 to 24 years (median 5.0). Characteristics of patients according to the disease course prior transplantation is given in Table 1.

Neurological assessment using EDSS and QoL assessment using RAND SF-36 questionnaire [19] was performed at baseline; at discharge; at 3, 6, 9, and 12 months after transplantation; every 6 months thereafter up to 48 months; and then at yearly intervals. MRI scans of the brain and spinal cord with gadolinium enhancement were performed at baseline; at 3, 6, and 12 months after transplantation; every 6 months thereafter up to 48 months; and then at yearly intervals.

Hematopoietic stem cells were mobilized with granulocyte colony-stimulating factor at 10 mg/kg according to EBMT/European League Against Rheumatism guidelines. Methylprednisolone as intravenous infusion, dose 250–500 mg daily for 5 days, was used to prevent disease flare.

Table 1 Characteristics of patients according to the disease course prior HDIT + AHSCT

	Relapsing/remitting MS (RRMS)	Secondary progressive MS (SPMS)[a]	Primary progressive MS (PPMS)	Progressive relapsing MS (PRMS)
Number of patients	43	35	18	3
Male/female	17/26	12/23	9/9	1/2
Mean age at the time of AHSCT, years (min–max)	32.7 (18–51)	35.9 (18–54)	36.7 (20–53)	36.6 (31–47)
Median EDSS at baseline (min–max)	1.5 (1.5–4.5)	5.0 (2.0–8.5)	4.5 (3.0–8.0)	6.0 (6.0–7.0)
Median MS duration, years (min–max)	4 (0.5–10)	9.5 (2.5–24)	7 (0.5–13)	10 (5–10)

[a] One patient with EDSS 8.0 at baseline examination worsened by the time of transplantation to EDSS 8.5

The mobilized cells were collected by apheresis, until a yield of at least 2×10^6 per kg CD34+ cells was obtained. The grafts were not manipulated. Unmanipulated peripheral blood stem cells were cryopreserved in standard conditions. Reduced-intensity conditioning regimen based on BEAM, i.e., low-intensity conditioning [20] was used. It included BCNU/CCNU 300 mg/m^2 and melphalan 50–100 mg/m^2 (BM) or BCNU/CCNU 300 mg/m^2, etoposide 75–100 mg/m^2, Ara-C 75–100 mg/m^2, and melphalan 50–100 mg/m^2 (mini BEAM-like). Sixty patients were conditioned with BM, others with mini BEAM-like. On day 0, frozen peripheral blood stem cells were thawed and reinfused intravenously with/without horse ATG (ATGAM, Pharmacia & Upjohn Company, Peapack, NJ, USA) in a dose of 30 mg/kg on days 1 and 2 for in vivo T cell depletion. During conditioning and thereafter till discharge, all the patients received standard supportive care.

Toxicity was evaluated in accordance with the National Cancer Institute common toxicity criteria, version 2. Neutrophil engraftment was defined as the first day after transplantation when the absolute neutrophil count was greater than 500 cells per ml. Platelet engraftment was defined as the first day after transplantation when the platelet count was greater than 20,000 platelets per ml without platelet transfusion.

According to the EBMT criteria of response, patients with either steady EDSS scores representing a halt of disease progression or with improved EDSS scores representing subsidence of inflammation in the CNS were regarded as responding to treatment [6]. Improvement in neurological function was defined as a decrease in the EDSS score of at least 0.5 points on two consecutive visits 3 months apart as compared with the baseline. Disease stabilization was defined as no changes in EDSS score during follow-up. Disease progression was defined an increase in the EDSS score of 0.5 points or more on a minimum of two occasions that were at least 3 months apart. A relapse of MS was defined as an acute deterioration in neurological function that lasted for more than 24 h without intercurrent illnesses or other causes for neurological impairment and with objective changes on neurological examination. Patients who relapsed or progressed after HSCT received specific therapy and were excluded from the study.

Transplant-related mortality definition included every death occurring within 100 days from transplantation [8].

For the analysis of time-to-event data, Kaplan–Meier methods were applied. Event-free survival rates and cumulative incidence of disease progression were calculated. Event-free survival is defined as freedom from any progression or relapse, with censoring of patients who are lost to follow-up. To calculate the cumulative incidence of disease progression, patients who experienced disease progression at any time after enrollment were included.

Comparisons were made via the log-rank test. QoL data were analyzed using the Friedman repeated measure analysis of variance on ranks.

Outcomes are reported as of April 2014, based on the last follow-up of each patient.

Results

Safety

No toxic deaths were reported among 99 MS patients treated with reduced-intensity BEAM-like regimen without graft manipulation, irrespective of their clinical condition at the time of transplant. Transplantation procedure was well tolerated by the patients. Mobilization was successful in all cases with a median number of 2.1×10^6/kg (range $1.5–5.5\times10^6$/kg) collected CD34+ cells; no major clinical adverse events were observed during this phase.

No deaths were registered throughout the entire follow-up period.

Efficacy

The median follow-up in the whole group was 48.9 months. Neurological examination at 6 months post-transplant demonstrated that EDSS either decreased or did not change in all the patients except one (PPMS, EDSS increased from 6.0 at baseline to 6.5 at 6 months post-transplant); thus, nearly all the patients responded to the treatment. Cumulative

incidence of patients experiencing disease progression is presented on Fig. 1.

At 8 years after HDIT + AHSCT, 16.7 % have progressed [95 % CI 3.7–38.0]. In the group with RRMS, 13.2 % [95 % CI 0.14–53.5] of patients have progressed; in the group with progressive disease course, 21.3 % [95 % CI 4.4–46.4] of patients experienced disease progression (Fig. 2).

Differences were not statistically significant ($p>0.05$). Median time to disease progression was 36 months (range 6.0–60.9). It was much higher in RRMS than in PrMS: 58 months (42.0–60.9) vs 24 months (6.0–42.0). Estimated event-free survival for the whole group of patients at median follow-up of 48.9 months was 80 % [95 % CI 67.6–88.1 %] (Fig. 3). Event-free survival curves for RRMS and PrMS are presented on Fig. 4.

In the group with RRMS, event-free survival rate was 83.3 % [95 % CI 59.4–93.8] and in the group with progressive course—75.5 % [95 % CI 58.0–86.5]; differences were not statistically significant ($p>0.05$). Event-free survival curves for two conditioning regimens—mini BEAM-like and BM—are presented on Fig. 5.

In the group receiving mini BEAM-like conditioning, event-free survival rate at median follow-up of 48.9 months was 85.5 % [95 % CI 61.3–95] and in the group receiving BM conditioning—79.5 % [95 % CI 64.3–88.7]; differences were not statistically significant ($p>0.05$).

No active, new, or enlarging lesions were registered in patients without disease progression.

Long-term outcome analysis was performed in 64 patients with at least 36 months follow-up post-transplant. The median follow-up in this group was 62 months (36–95 months). Other 35 patients were not included in the analysis because of less than 36 months after HDIT + AHSCT or due to disease progression or relapse in earlier period; in addition, several patients were lost between 12 and 36 months post-transplant. Out of 64 patients, 30 (47 %) improved by at least 0.5 point on the EDSS scale as compared to baseline and exhibited

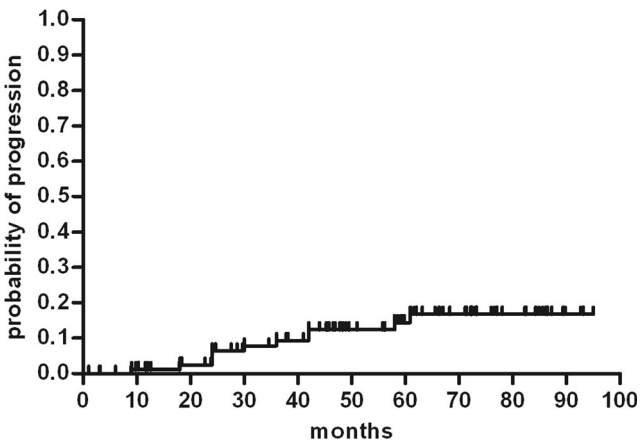

Fig. 1 Probability of disease progression in MS patients undergoing HDIT + AHSCT (median follow-up—48.9 months)

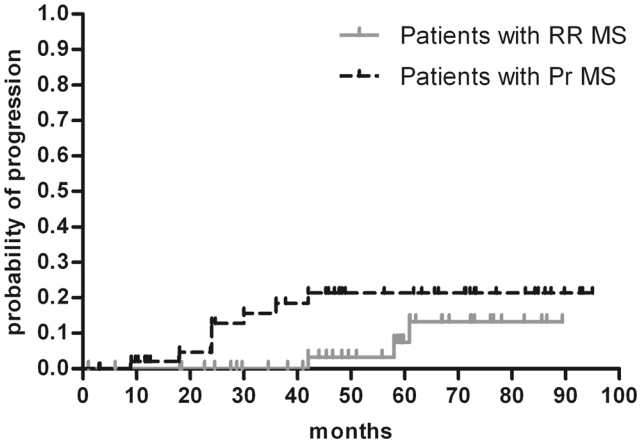

Fig. 2 Probability of disease progression in patients with relapsing-remitting and progressive MS undergoing HDIT + AHSCT (median follow-up—48.9 months)

improvement during the entire period of follow-up. Among them, there were 14 RRMS, 4 PPMS, and 12 SPMS. Twenty-nine patients were stable: 17 RRMS, 4 PPMS, 7 SPMS, and 1 PRMS. Three patients with RR course experienced worsening at 42, 60, and 66 months after HDIT + AHSCT, correspondingly. The vast majority of RRMS patients, who did not progress, were relapse-free (29 out of 31). Two patients with progressive disease worsened at 36 and 42 months after HDIT + AHSCT, correspondingly. Remarkably, all patients who did not have disease progression or relapse were off therapy throughout the post-transplant period.

Results of MRI scans at long-term follow-up were available in 55 patients. Fifteen patients (27 %) had active lesions at baseline and 40 patients were without active lesions pre-transplant. At 6 months after HDIT + AHSCT in the group of patients with active lesions, all turned to inactive status except one case; in the group without active lesions pre-transplant, 39 remained inactive, whereas one patient showed disease activity. At the median of 26 months post-transplant in the group with Gd-enhancing lesions at baseline, three cases of disease progression were registered: in two patients, new active lesions appeared at 24 and 42 months post-transplant; one patient progressed without new or enlarging lesions at MRI. In the group without active lesions at baseline, also three patients progressed: in two patients, Gd-enhancing lesions appeared at 9 and 42 months post-transplant; in one patient disease progressed without new or enlarging lesions. No active, new, or enlarging lesions were registered in patients without disease progression/relapse. The analysis to identify if there were differences in treatment outcomes depending on the presence/absence of Gd-enhancing lesions at baseline was not done due to the small number of cases of progression.

Quality of life

QoL monitoring during the entire study period was performed in 49 patients: 24 RRMS and 25 PrMS. Remarkable

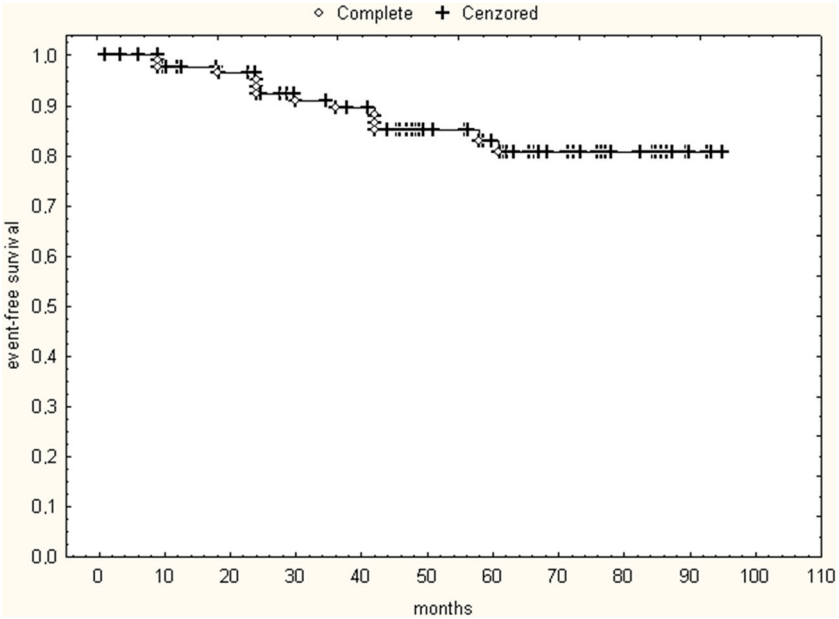

Fig. 3 Event-free survival time in MS patients after HDIT + AHSCT (median follow-up—48.9 months)

improvement of QoL scales was observed. QoL profiles demonstrate positive changes in patient's QoL 1 year post-transplant both in RRMS and in PrMS (Figs. 6 and 7). QoL improvement was more dramatic in RRMS: we found a significant increase of all eight SF-36 scales in a year post-transplant as compared with baseline ($p<0.05$). In PrMS, statistically significant improvement was registered for six out of eight SF-36 scales (except bodily pain and role-emotional functioning) ($p<0.05$). At it is seen from Figs. 6 to 7, at long-term follow-up, the values of SF-36 scales were much higher as compared with pre-transplant ones and were similar to the ones in a year post-transplant. Improved QoL parameters were preserved over the entire study period in all the patients who did not have disease progression or relapse.

Discussion

During the last two decades, HDIT + AHSCT has been used as a treatment option for MS with promising outcomes. The mechanism by which AHSCT exerts the effect in MS has not been fully resolved. It is well established that AHSCT causes a profound and prolonged immunosuppression. Moreover, it is thought that AHSCT induces a number of qualitative

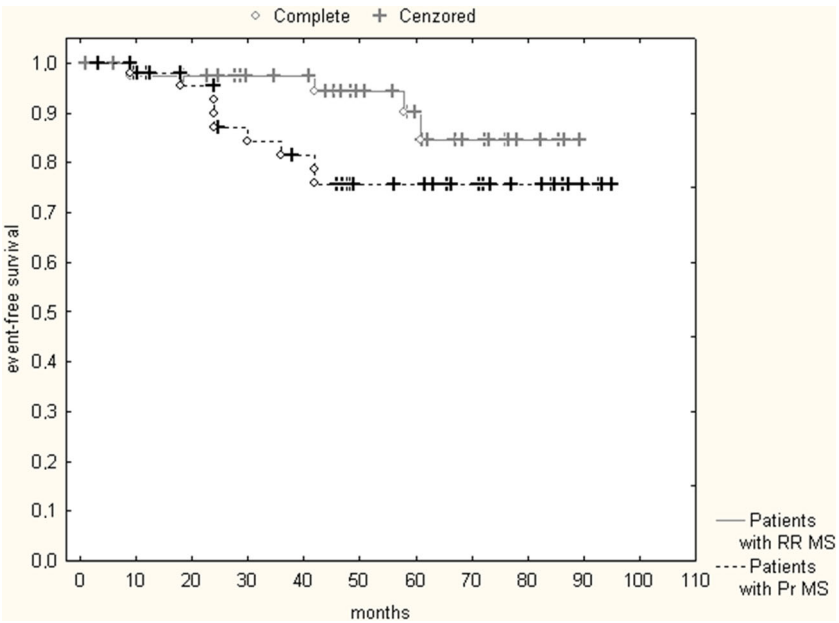

Fig. 4 Event-free survival time in patients with relapsing-remitting MS and progressive MS after HDIT + AHSCT (median follow-up—48.9 months)

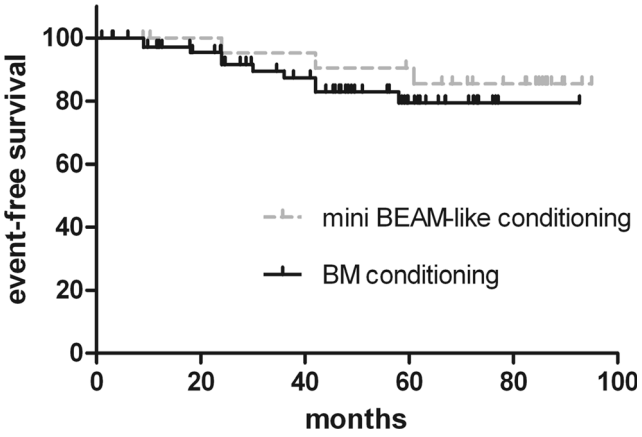

Fig. 5 Event-free survival time in MS patients receiving different conditioning regimens

immunologic changes and, in doing so, ablation of the aberrant immune system followed by reconstitution of the new immune system from hematopoietic stem cells may alter the characteristics of the T cell responses and other immunological properties, which may improve the clinical course of MS.

Recent reviews evaluated the evidence concerning the safety and efficacy of HDIT + AHSCT in MS patients [21–24]. The benefits of HDIT + AHSCT in MS have been demonstrated both in single-center studies and multi-center cooperative studies [8–10, 17, 25–29]. However, the treatment is associated with a number of side effects, and of major concern is the transplant-related mortality. In regard to this, the choice of a conditioning regimen is the crucial issue for HDIT + AHSCT. At present, the most promising results of HDIT + AHSCT have been obtained with BEAM as a conditioning regimen [20–24, 30, 31]. According to EBMT data from years 2001–2006, mortality in MS patients treated with intermediate-intensity conditioning regimens is 0.9 % [32]. Taking into account these data and serious concerns of neurological community that HDIT + AHSCT is associated with the risk of mortality and adverse effects, we proposed a new reduced-intensity conditioning regimen based on BEAM. We have reported our initial finding earlier [12]. Long-term follow-up is of importance to better evaluate treatment outcomes of HDIT + AHSCT. There are few published data on the outcomes of HDIT + AHSCT based on BEAM as conditioning regimen with a median follow-up of ≥4 years [27–29]

In our study, quite a large cohort of patients, namely 99 MS patients with various types of disease course, was analyzed. As a result, transplantation procedure was well tolerated by the patients, with no transplant-related deaths. Remarkably, no deaths were registered in this group during the entire period of follow-up. Cumulative incidence of disease progression was 16.7 % at 8 years after HDIT + AHSCT with reduced-intensity conditioning regimen based on BEAM. Estimated event-free survival at median follow-up of 48.9 months was 80 %. These promising results might be due to the fact that our cohort of patients was relatively young (mean age—35 years old) and not very disabled (median EDSS—3.5). It is in line with the suggestion that the best candidates for transplantation seem to be relatively young patients with active inflammatory lesions of relatively short duration and rapidly progressive disease, but still low disability scores, unresponsive to conventional therapy [16]. In our study, similar outcomes were observed in the groups with both types of conditioning (BN and mini BEAM-like). These data strongly support the use of reduced-intensity BEAM-like conditioning regimen for HDIT + AHSCT.

The advantage of our study is that we included patients with different types of MS. It was demonstrated that HDIT + AHSCT may be effective in patients with both remitting and progressive course of the disease. Cumulative incidence of disease progression was quite low both for RRMS and

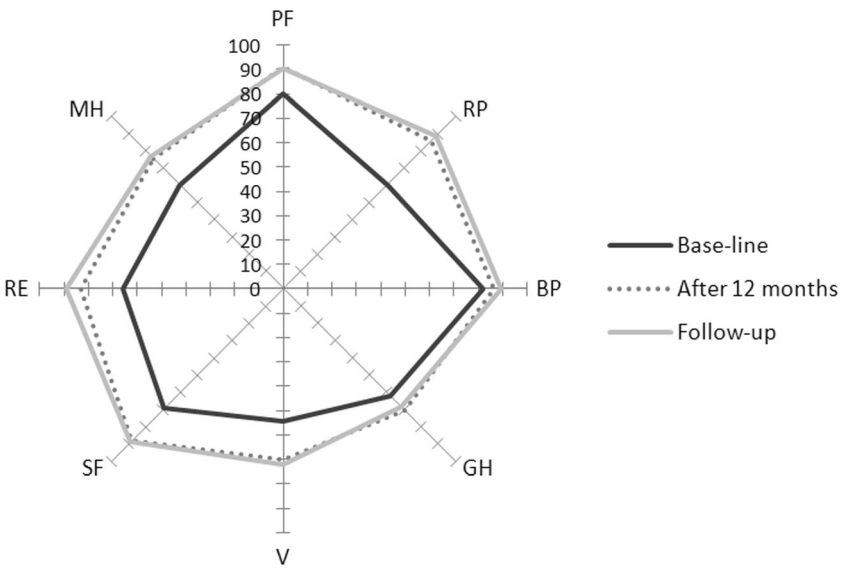

Fig. 6 Quality of life profiles in patients with relapsing-remitting MS before and at different time points after HDIT + AHSCT. *PF*, physical functioning; *RF*, role-physical functioning; *BP*, bodily pain; *GH*, general health; *VT*, vitality; *SF*, social functioning; *RE*, role-emotional functioning; *MH*, mental health

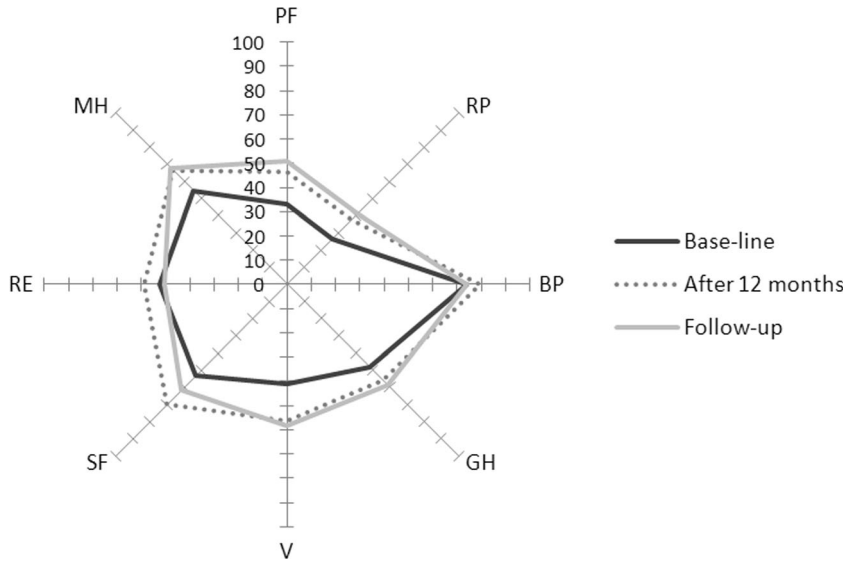

Fig. 7 Quality of life profiles in patients with progressive MS before and at different time points after HDIT + AHSCT. *PF*, physical functioning; *RF*, role-physical functioning; *BP*, bodily pain; *GH*, general health; *VT*, vitality; *SF*, social functioning; *RE*, role-emotional functioning; *MH*, mental health

PrMS. It was higher in patients with progressive course of the disease than in those with relapsing/remitting MS: 21.3 vs 13.2 %. However, the differences were not statistically significant. During the first 3 post-transplant years, the event-free survival rates were much higher for RR MS than in those with progressive course of the disease. In our previous study, statistically significant differences were observed between the groups. At longer follow-up, differences became less remarkable. In the group with RRMS, event-free survival rate at median follow-up of 48.9 months was 83.3 % and in the group with progressive course—75.5 %. Our results are comparative with the published data [10, 14, 16, 33].

Of special interest in our study was the analysis of long-term outcomes. Sixty-four patients who did not progress during the first 3-year post-transplant and were monitored for more than 3 years were included in the analysis. The median long-term follow-up in this cohort was 62 months. Among them, 47 % of patients improved by at least 0.5 points on the EDSS scale as compared to baseline and exhibited improvement during the entire period of follow-up; 45 % of patients were stable. These results point that reduced-intensity BEAM-like conditioning regimen has long-term effect in MS patients. To note, at long-term follow-up, 92 % of patients with different types of MS exhibited either improvement or were stable. Among 64 patients included in long-term outcomes analysis, three patients with RR course experienced worsening at 42, 60, and 66 months after HDIT + AHSCT, respectively; two patients with progressive disease worsened at 36 and 42 months post-transplant, respectively. The vast majority of RRMS patients, who did not progress, were relapse-free. Notably, all patients without disease progression were off therapy throughout the post-transplant period. Thus, in the group of patients, who did not worsen during the first 3 post-transplant years, the vast majority demonstrated either improvement or were stable during the entire period of follow-up. This is true both for patients with relapsing/remitting MS and for patients with progressive course of the disease.

Another advantage of our study is that we included patients both with active CNS disease pre-transplant (40 %) and those without. The latter ones did not have active lesions on MRI but they experienced clinical worsening and progression of disability. The outcomes of our study showed that patients both with active CNS disease and those without may benefit from transplantation.

It can be explained by the presence of occult inflammation not detectable with conventional MRI. In this situation, we consider that neurological progression even in the case of the absence of active lesions may be indication for HDIT + AHSCT.

Finally, we have performed comprehensive analysis of long-term outcomes of HDIT + AHSCT. In addition to clinical outcomes, we studied patient-reported outcomes, namely the QoL changes after HDIT + AHSCT. QoL is an important outcome of MS treatment and its assessment provides the patient's perspective on the overall effect of treatment and allows for evaluation of patient benefits. Our results definitely show that AHSCT resulted in significant improvement of patient's QoL. Improvement was demonstrated at long-term follow-up both for the group with RRMS and for those with progressive course of the disease.

The study has a number of limitations. The patients enrolled in the study previously have been treated in different centers, and the information about disease activity prior in the disease course and its treatment was inhomogeneous and in some cases quite scarce. Another limitation deals with the fact that patient selection was to some extent different to other studies, namely in our group patients had milder disease. Thus, comparison of the results obtained in this study with the results in the literature should be done with caution. In

addition, similar to other published reports, there was absence of a control group and that study visits after 1 year post-transplant were less frequent and more irregular so that the use of confirmed disability as the EDSS-failure end-point was more problematic.

In conclusion, the consistency of our clinical and QoL results, together with the persistence of improvement at long-term follow-up, is in favor of the efficacy of HDIT + AHSCT in MS patients. The results of our study support the feasibility of reduced-intensity condition regimen based on BEAM. Overall, HDIT + AHSCT with reduced-intensity condition regimen may be beneficial for patients with various types of MS. Multicenter cooperative studies are needed for better assessment of treatment outcomes. Further studies are necessary to develop proper criteria for the candidates for HDIT + AHSCT with reduced-intensity conditioning regimens.

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Conflict of interest No financial interest/relationships with financial interest relating to the topic of this article have been declared.

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