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Research Article

Clinical and Patient-Reported Outcomes of Autologous Hematopoietic Stem Cell Transplantation (AHSCT) In Patients with Multiple Sclerosis: Single Center Experience

Vladimir Y Melnichenko[1], Tatiana I Ionova[2], Tatiana P Nikitina[2], Ilya S Nikolaev[1], Anastasia K Panchenko[1], Natalia M Porfirieva[3], Anatoliy A Rukavitcyn[1] and Denis A Fedorenko[1]*

[1]Department of Hematology, Chemotherapy and Bone Marrow Transplantation, Pirogov National Medical and Surgical Center, Moscow, Russia

[2]Clinic of High Medical Technologies named after N.I. Pirogov, Saint-Petersburg State University Hospital, Saint-Petersburg, Russia

[3]Multinational Center for Quality-of-Life Research, Saint-Petersburg, Russia

***Corresponding Author:** Denis A Fedorenko, Department of Hematology, Chemotherapy and Bone Marrow Transplantation, Pirogov National Medical and Surgical Center, Moscow, Russia.

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Abstract

The effect of HDIT + AHSCT with low-intensity conditioning regimens in patients with various types of multiple sclerosis (MS) in terms of clinical and patient-reported outcomes was studied. In total, 418 patients with relapsing-remitting (RRMS) and secondary progressive MS (SPMS) were enrolled in a single-center study from October 2006 to October 2018. Median follow-up was 29.8 months. Outcomes of AHSCT were evaluated both from physician's and patient's perspective at 3, 6, 12 months after AHSCT and at long-term follow-up. EDSS changes, proportion of patients who achieved NEDA-3, event-free survival (EFS), safety, and quality of life (QoL) changes were evaluated separately in patients with RRMS and SPMS. Paired t-test, Wilcoxon test and Generalized Estimating Equations and were used for comparisons. Kaplan-Meyer method was used to evaluate EFS in terms of relapse-free survival (RFS) and progression-free survival (PFS) after AHSCT. Good tolerability of transplantation procedure was demonstrated in both patient groups. There were no cases of transplantation-related mortality. Response to treatment was achieved in the vast majority of patients. Significant improvement in disability for the entire group at all time-points after transplantation as compared with baseline was observed. The EDSS score improved in 32% and 17% of RRMS patients and in 32% and 36% SPMS patients, at 2 years and 4 years, respectively. At follow-up of 12 months postransplant, 94.6% RRMS patients and 85.6% SPMS patients achieved NEDA-3. At 7-year follow-up after AHSCT the estimated RFS in RRMS were 83%; PFS in SPMS was 77%. No differences in EFS were found according to conditioning regimens in both RRMS and SPMS. EFS in RRMS and SPMS was similar in the subgroups of patients depending on age and disease duration. RFS was dramatically better in patients with EDSS < 4 as compared to patients with EDSS ≥ 4 in RRMS patients; no differences were shown for PFS in SPMS patients depending on EDSS. In terms of patient's perspective AHSCT resulted in significant and sustained improvement of patient's QoL both in RRMS and SPMS. The results obtained point to feasibility of AHSCT with low-intensity conditioning regimens in RRMS and SPMS patients. Multicenter cooperative studies are worthy to optimize the protocol of AHSCT with low-intensity conditioning regimens in patients with MS.

Keywords: Autologous Hematopoietic Stem Cell Transplantation; Low-Intensity Conditioning Regimens; Relapsing-Remitting Multiple Sclerosis; Secondary Progressive Multiple Sclerosis; Quality of Life

Abbreviations

MS: Multiple Sclerosis; CNS: Central Nervous System; RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; HDIT: High-Dose Immunosuppressive Therapy; AHSCT: Autologous Hematopoietic Stem Cell Transplantation; DMT: Disease-Modified Treatment; G-CSF: Granulocyte Colony-Stimulating Factor; QoL: Quality of Life; NEDA: No Evidence of Disease Activity; EDSS: Expanded Disability Status Scale; MRI: Magnetic Resonance Imaging; TRM: Transplantation-Related Mortality; RFS: Relapse-Free Survival; PFS: Progression-Free Survival; EFS: Event-Free Survival; ANOVA: Analysis of Variances; PF: Physical Functioning; RPF: Role Physical Functioning; BP: Bodily Pain; GH: General Health; V: Vitality; SF: Social Functioning; REF: Role Emotional Functioning; MH: Mental Health

Introduction

Multiple sclerosis (MS) is a major inflammatory and demyelinating disease of the central nervous system (CNS) [1,2]. It affects mainly young people and is accompanied with progressive deterioration of quality of life (QoL) due to progressive disability [1-3]. MS patients suffer from a variety of symptoms which have negative impact on patient's QoL. Noteworthy, the degree of impact of MS on patient's well-being should be considered in terms of patients' own perceptions of those impacts. Relapsing-remitting MS (RRMS) transfers to secondary progressive disease in 70-80% of cases during 10-15 years [4,5]. So, favorable variant of MS seems to be very difficult condition with high risk of disability. Thus, the goal of treatment is to prevent MS progression and disability, better symptoms control and patient's QoL improvement. By now MS is incurable disease. Modern disease-modified treatment (DMT) is limited to prevent MS progression and finally critical disability [6,7]. Conventional DMT does not control MS satisfactory as it is not able to eradicate self-aggressive T- and B-cell clones. Immunosuppressive treatment or monoclonal antibodies, which are usually used as a second-line therapy, also have only partial beneficial effect.

At present high-dose immunosuppressive therapy (HDIT) with autologous hematopoietic stem cell transplantation (AHSCT) has been frequently used as a therapeutic option for patients with MS [8-15]. The rationale of HDIT + AHSCT is that ablation of aberrant immune system followed reconstitution of the new immune system may alter the characteristics of the T-and B-cell responses and other immunological properties and in doing so lead to improvement of clinical course of MS. In the previous studies it was shown that AHSCT was associated with improvement in neurological disability and QoL in patients with RRMS [16-17]. AHSCT is a valuable option in aggressive RRMS. Its efficacy in secondary progressive MS (SPMS) is still controversial though for some patients benefits of AHSCT were shown [17-21].

At the same time, in spite of promising clinical results, there are still several questions to be clarified before recommending AHSCT as a treatment choice for MS patients. To note, effectiveness and safety of different conditioning regimens, namely intermediate and low-intensity ones, should be analyzed carefully. Several clinical studies have been focused on safety and effectiveness of AHSCT with BEAM as intermediate-intensity conditioning regimen in MS and promising results were obtained [22-24]. Furthermore, it was demonstrated recently, that low-intensity regimens (BEAM-like or Cyclophosphamide based) may result in similar outcomes and less toxicity profile as compared with more intensive conditioning. Another important issue is patients' selection for AHSCT [12,25,26]. Finally, comprehensive assessment of treatment outcomes is worthy for AHSCT with different conditioning regimens [27,28]. Both disease-free period and improvement of patient's QoL are recognized as valuable treatment outcomes. Also, one of the key issues is the long-term follow-up assessment of clinical and patient-reported outcomes [15,28-30]. For patients with MS both disease-free period and improvement of patient's QoL are recognized as important outcome parameters. With this in mind, single-center study of the use of AHSCT with different low-intensity conditioning regimens in MS with various types of disease was initiated.

In this paper we report the outcomes of HDIT + AHSCT with reduced intensity regimens based on BEAM and Cyclophosphamide in patients with MS with different course of the 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 RRMS and SPMS was carried out.

Materials and Methods

All the patients underwent AHSCT in the Transplantation Unit of the Department of Hematology and Cellular Therapy, Pirogov's National Medical and Surgical Center (Moscow) from October 2006 to October 2018. The follow-up period lasted till 1 August 2019. The study was performed in accordance to the principles of the Helsinki Declaration, and was approved by the Institute Research Board and local Ethics Committee before initiation. Written informed consent was obtained from all the patients. Patients were

eligible if they were aged > 15 years old and met the McDonald criteria for clinically definite MS [31]. Other criteria for patient selection were normal mental status; and absence of severe concomitant diseases. The vast majority of patients were refractory to 2-4 different variants of conventional treatment including interferons, copaxone, mitoxantrone, cladribine, monoclonal antibodies therapy, azathioprine, intravenous immunoglobulin, steroids and other.

Hematopoietic stem cells were mobilized with granulocyte colony-stimulating factor (G-CSF) 10 mg/kg during 4-5 days. The mobilized cells were collected by apheresis after 4 days of stimulation until a yield of at least 2.0 x 10^6/kg CD34 + cells.

Three low-intensity regimens were applied. The two ones were based on reduced BEAM

BM (BCNU 300 mg/m^2, Melphalan 100 mg/m^2 ± horse ATG in dose 30 mg/kg on days 1 and 2 for *in vivo* T cell-depletion) and BEAM-like (BCNU 300 mg/m^2, Etoposide 100 mg/m^2, Ara-C 100 mg/m^2, Melphalan 100 mg/m^2 ± horse ATG in dose 30 mg/kg on days 1 and 2 for *in vivo* T cell-depletion). The third one was high-dose Cyclophosphamide: Cyclophosphamide 200 mg/kg + Rituximab 500 mg/m^2 on D + 11-12 (one infusion).

Five micrograms per kilogram G-CSF were administered from D + 1-D + 2 till granulocyte recovery. For infection prophylaxis oral levofloxacin, fluconazole, co-trimoxazole and acyclovir were used.

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria (version 2) [32]. Neutrophil engraftment was defined as the first day after transplantation when absolute neutrophil count was > 500 cells/mL. Platelet engraftment was defined as the first day after transplantation when the platelet count was > 20 000 platelets/mL without platelet transfusion.

Transplantation-related mortality (TRM) definition included every death occurring within 100 days of transplantation [33].

The primary endpoint was disability measured using the EDSS score [34]. Other study endpoints included event-free survival (EFS), proportion of patients who achieved NEDA-3, safety, and quality of life (QoL) changes. EFS was considered as relapse-free survival (no acute relapses) for RRMS (RFS), and as progression-free survival for SPMS (PFS). No evidence of disease activity (NEDA) was referred broadly to stabilization of disease as evidenced by lack of clinical relapses, lack of disease progression measured by expanded disability status scale (EDSS) and absence of new disease activity (new T2 lesions/enhancing lesion) on magnetic resonance imaging (MRI) over a period of observation [35]. Data of neurological assessment and MRI scans were analyzed for clinical outcomes. Neurological assessment was performed at baseline, at discharge, 3, 6, and 12 months after transplantation, every 6 months thereafter up to 48 months, and then at yearly intervals. EDSS decrease of 1.0 or greater was considered as significant improvement and an increase of 1.0 or greater was considered as significant worsening. MRI scans of the brain and cervical spinal cord with gadolinium enhancement were performed at different time-points - at baseline, 3, 6, and 12 months after transplantation, every 6 months thereafter up to 48 months, and then at yearly intervals. For QoL assessment RAND SF-36 was used [36]. SF-36 is generic QoL assessment tool and is widely used in patients with chronic diseases, including MS [37,38]. Measurements were conducted before AHSCT, at 6 and 12 months after AHSCT, then every 6 months during 2 years after AHSCT and every 12 months after 2 years during 5 years after AHSCT.

For comparisons paired t-test, Wilcoxon test and Generalized Estimating Equations (GEE) were applied. Kaplan-Meyer method was used for evaluation of EFS in terms of RFS and PFS after AHSCT. For comparison of survival log-rank criterion and Tarone-Ware criterion were applied. P values of less than 0.05 were used as a cut-off point for statistical significance and all statistical tests were two-sided. Medcalc and IBM SPSS 23.0 softwares were applied.

Results and Discussion

In total, 418 patients with MS were enrolled into the study: 258 RRMS and 160 SPMS. Mean age - 38.3 years old; male/female - 139/279. Median EDSS before transplantation was 3.5 (range 1.5-8.5); mean duration of the disease was 6.9 years (range, 0.5-33). In the group with RRMS median EDSS before transplantation - 2.0 (range, 1.5-6.5); mean duration of the disease - 4.9 years (range, 0.5-24). In the group with SPMS median EDSS before transplantation - 6.0 (range, 1.5-8.5); mean duration of the disease was 10.5 years (range, 1.0-33). One hundred and forty-six patients (34.9%) had active lesions at baseline, among them 103 (24.6%) RRMS and 43 (10.3%) SPMS patients.

Efficacy

Median follow-up after AHSCT was 29.8 months (range, 0.2-110.9). EDSS score decreased after transplantation. Significant improvement in disability for the entire group at all time-points after transplantation as compared with baseline was observed (p

< 0.001). The decrease of EDSS in RRMS took place from median 2.0 to 1.5 at 12 months after AHSCT and in SPMS - from median 6.0 to 5.0 at 12 months after AHSCT. It preserved the same at long term follow-up of more than 60 months in patients with RRMS and exhibited further improvement in the group with SPMS (Figure 1 a, b).

Changes in EDSS in patients with RRMS and SPMS before and at different time-points after AHSCT are presented in tables 1 and 2. In the group with RRMS the proportion of patients with a 1.0 or greater change in EDSS score was 36% (86 patients) with an indication of improvement at 12 months and 0.4% (1 patient) with an indication of progression. At 2 years posttransplant 32% (47 patients) improved, 0.7% (1 patient) worsened and others were stable. At 3 years posttransplant improvement was observed in 25% (23 patients), worsening - in 1.1% (1 patient), others were stable. At 4 years posttransplant the majority (83.1%) of patients were stable, there was no worsening, and 16.9% (10 patients) exhibited improvement. At longer term follow-up the vast majority of patients were stable; worsening took place in 6% of patients. In the group with RRMS the proportion of patients with a 1.0 or greater change in EDSS score was 31% (45 patients) with an indication of improvement at 12 months and 4% (6 patients) with an indication of progression. At 2 years posttransplant 32% (26 patients) improved, 5% (4 patients) worsened and others were stable. At 3 years posttransplant improvement was observed in 33% (17 patients), worsening - in 2% (1 patient), others were stable. At 4 years posttransplant improvement was observed in 36% (12 patients), worsening - in 6% (2 patients), others were stable. At longer term follow-up the vast majority of patients were stable; worsening took place in 7% (1 patient).

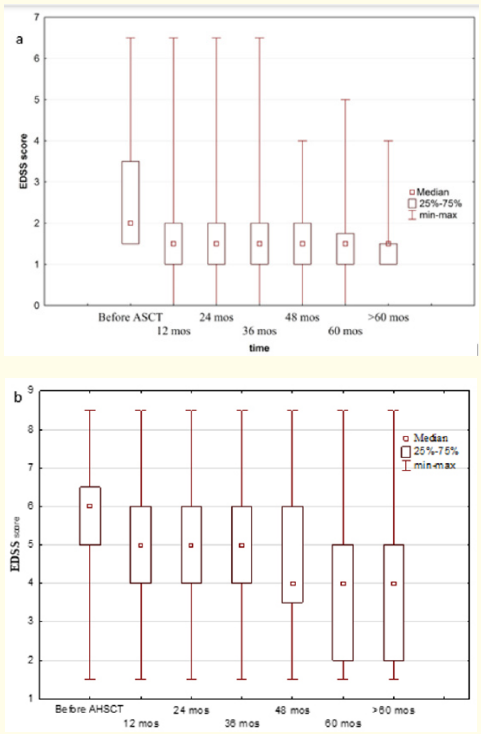

Figure 1: EDSS medians in patients with RRMS (a) and SPMS (b) before and at different time-points after AHSCT.

EDSS = Expanded Disability Status Scale; RRMS = Relapsing-Remitting Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; AHSCT = Autologous Hematopoietic Stem Cell Transplantation.

EDSS	Time-points						
	Before AHSCT	**12 mo**	**24 mo**	**36 mo**	**48 mo**	**60 mo**	**> 60 mo**
N	258	237	145	92	59	32	16
Median (interquar-tile range)	2.0 (1.5-3.5)	1.5 (1.0-2.0)	1.5 (1.0-2.0)	1.5 (1.0-2.0)	1.5 (1.0-2.0)	1.5 (1.0-0.75)	1.5 (1.0-1.5)
Mean, (SD)	2.6 (1.2)	1.68 (1.15)	1.60 (1.04)	1.75 (1.01)	1.60 (0.69)	1.64 (0.94)	1.50 (0.73)
95% CI	2.4-2.7	1.53-1.82	1.43-1.78	1.54-1.95	1.42-1.78	1.30-1.98	1.11-1.89
Type of EDSS changes, n (%)							
Stabilizati-on (change ≤ 0,5 score)		150 (63.3)	97 (66.9)	68 (73.9)	49 (83.1)	24 (75.0)	14 (87.4)
Improve-ment (≥ 1 score)		86 (36.3)	47 (32.4)	23 (25.0)	10 (16.9)	6 (18.8)	1 (6.3)
Worsening (≥ 1 score)		1 (0.4)	1 (0.7)	1 (1.1)	-	2 (6.2)	1 (6.3)

Table 1: EDSS changes in patients with RRMS before and at different time-points after AHSCT.

EDSS: Expanded Disability Status Scale; RRMS: Relapsing-Remitting Multiple Sclerosis; CI: Confidence Interval; SD: Standard Deviation; AHSCT: Autologous Hematopoietic Stem Cell Transplantation

EDSS	Time-points						
	Before AHSCT	12 mo	24 mo	36 mo	48 mo	60 mo	> 60 mo
N	160	144	82	52	33	18	15
Median (interquartile range)	6.0 (5.0-6.5)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	4.0 (3.5-6.0)	4.0 (2.0-5.0)	4.0 (2.0-5.0)
Mean, (SD)	5.6 (1.1)	5.0 (1.5)	4.9 (1.6)	4.7 (1.6)	4.5 (1.8)	3.9 (1.9)	4.1 (1.9)
95% CI	1.01-1.25	1.35-1.71	1.35-1.83	1.36-2.04	1.48-2.43	1.40-2.79	1.41-3.04
Type of EDSS changes, n (%)							
Stabilization (change≤0,5 score)		94 (65.3)	52 (63.4)	34 (65.4)	19 (57.6)	11 (61.1)	8 (53.3)
Improvement (≥ 1 score)		45 (31.3)	26 (31.7)	17 (32.7)	12 (36.3)	7 (38.9)	6 (40.0)
Worsening (≥ 1 score)		5 (3.4)	4 (4.9)	1 (1.9)	2(6.1)	-	1 (6.7)

Table 2: EDSS changes in patients with SPMS before and at different time-points after AHSCT.

EDSS: Expanded Disability Status Scale; SPMS: Secondary Progressive Multiple Sclerosis; CI: Confidence Interval; SD: Standard Deviation; AHSCT: Autologous Hematopoietic Stem Cell Transplantation

After AHSCT the vast majority of patients with RRMS were relapse-free (245 out of 258). Mean time until relapse was 30.4 months (95% CI 18.24-42.52). Estimated RFS at the follow-up of 36 months was 95.6% (95% CI: 92.4-98.8), at the follow-up of 60 months - 88.2% (95% CI: 80.2-96.2); at the follow-up of 84 months - 83.3% (95% CI: 71.3-95.3), (Figure 2).

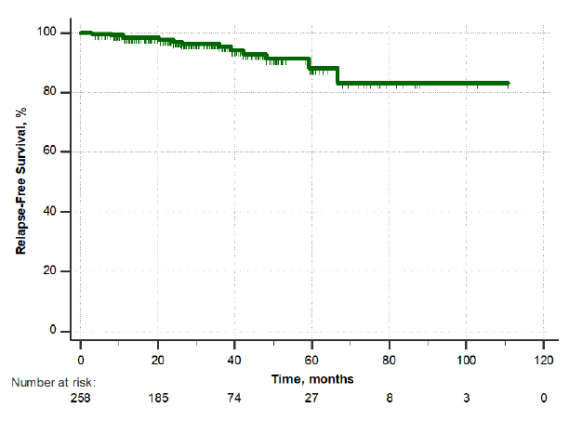

Figure 2: Relapse-free survival Kaplan-Meyer curve in RRMS patients after AHSCT.

Estimated PFS in SPMS at the follow-up of 24 months was 88.1% (95% CI: 83.0-94.0), at the follow-up of 36 months - 87% (95% CI: 81.0-93.0), at the follow-up of 84 months - 76.5% (95% CI: 66.0-87.0), (Figure 3).

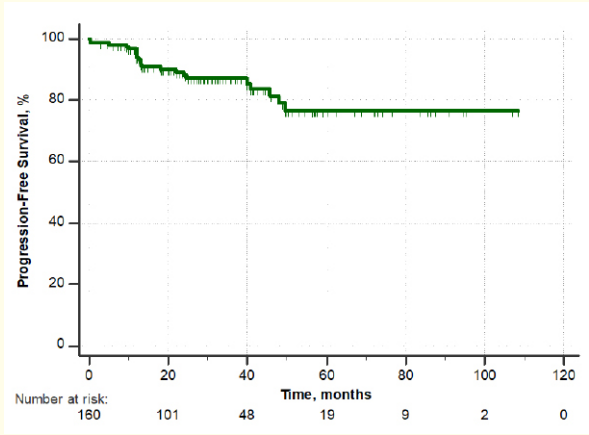

Figure 3: Progression-free survival Kaplan-Meyer curve in SPMS patients after AHSCT.

Noteworthy, no active, new or enlarging lesions were registered in RRMS patients who were relapse free and in SPMS without disease progression. At follow-up of 12 months postransplant, 244 (94.6%) RRMS patients and 137 (85.6%) SPMS patients achieved NEDA-3.

Separate analysis for probability of EFS in the groups of patients with different conditioning regimens was performed. Comparison was made between the conditioning regimens based on BEAM-like and Cyclophosphamide + Rituximab. Previously it was shown that the outcomes for mini-BEAM and BM were similar [28], thus

the group BEAM-like included mini-BEAM and BM conditioning regimens. No differences in RFS for RRMS and PRS for SPMS were found between patients who received BEAM-like and those who received high-dose Cyclophosphamide + Rituximab (log-rank, p = 0.92 and p = 0.125), (Figure 4 a, b).

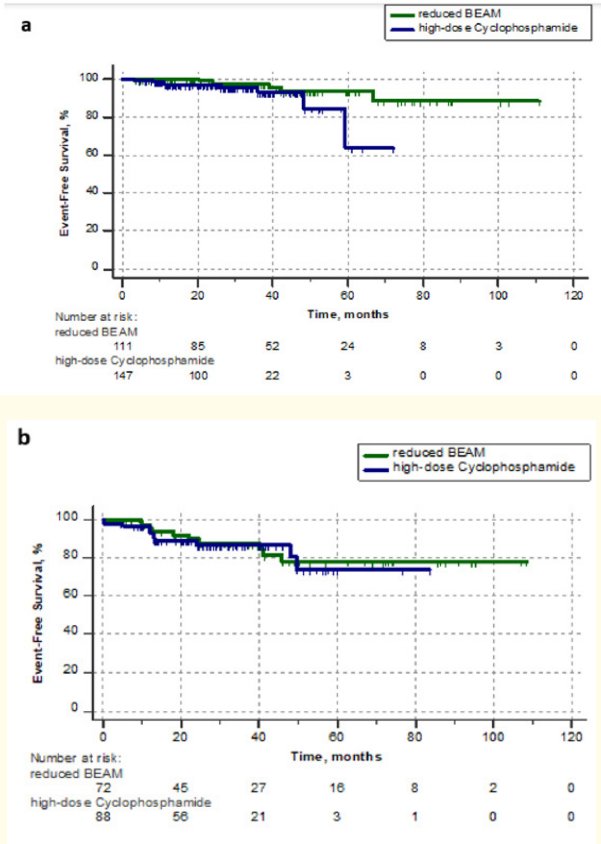

Figure 4: Event-free survival Kaplan-Meyer curves for RRMS (a) and SPMS (b) who received BEAM-like and who received high-dose Cyclophosphamide + Rituximab.

Further analysis for probability of EFS was performed for the subgroups of patients with different age, EDSS and disease duration. RFS Kaplan-Meyer curves for RRMS patients younger 30 years old and aged ≥ 30 years old are presented in figure 5, a. No differences in RFS were found between these age groups (log-rank, p = 0.709). The differences in RFS were also not statistically significant between patients with disease duration less 5 years and disease duration ≥ 5 years (log-rank, p = 0.763), figure 5, b. As for disability status, RFS was dramatically better in patients with EDSS < 4 as compared to patients with EDSS ≥ 4 (log-rank, p = 0.049; Tarone-Ware, p = 0.048), (Figure 5),

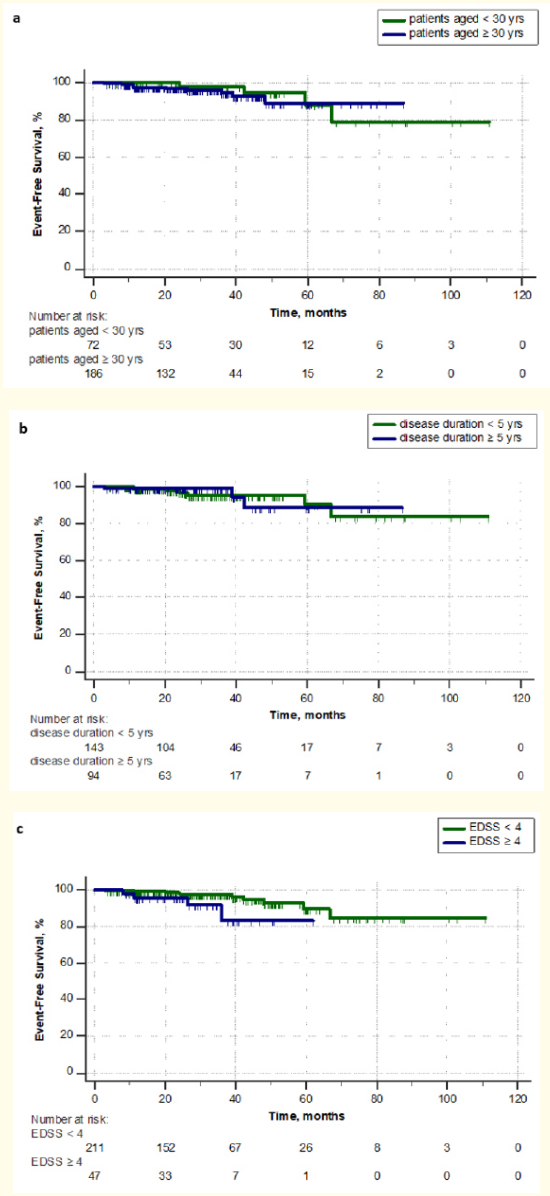

Figure 5: EFS Kaplan-Meyer curves for different groups of RRMS patients: patients aged < 30 years and patients aged ≥ 30 years (a); patients with disease duration < 5 years and disease duration ≥ 5 years (b); patients with EDSS < 4 and with EDSS ≥ 4 (c).

EFS Kaplan-Meyer curves for SPMS patients depending on age, disease duration and baseline EDSS are presented in figure 6. Interestingly, PFS at 60 months was better in patients of younger age, with less disease duration and lower EDSS, though these differences were not statistically significant. PFS was 87.9% (CI: 72-100) in patients aged < 30 years vs 74.3% (CI: 62-86) in patients aged ≥ 30 years (log-rank, p = 0.442), 95.5% (CI: 87-100) in patients with disease duration < 5 years vs 76.6% (CI: 62-86) in patients with disease duration ≥ 5 years (log-rank, p = 0.221), 92.7% (CI: 83-100) in patients with EDSS < 5 vs 71.3% (CI: 58-84) in patients with EDSS ≥ 5 (log-rank, p = 0.151).

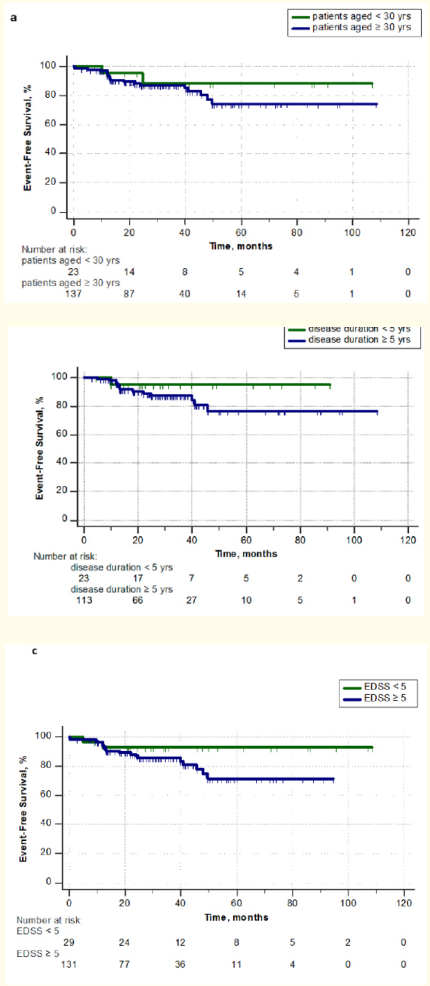

Figure 6: EFS Kaplan-Meyer curves for different groups of SPMS patients: patients aged < 30 years and patients aged ≥ 30 years (a); patients with disease duration < 5 years and disease duration ≥ 5 years (b); patients with EDSS < 5 and with EDSS ≥ 5 (c).

Safety

Transplantation procedure was well tolerated by the patients. There were no cases of transplantation-related mortality. Mobilization was successful in all cases with median number of 2.1 x 10^6/kg (range 2-10.9 x 10^6/kg) collected CD34 + cells; no major clinical adverse events were observed during this phase.

The mean time of neutropenia (grade 4) was 8.0 days. The mean time of thrombocytopenia (grade 3-4) - 7.0 days. Neutrophil engraftment was registered on D + 8- D + 11. No differences in hematological toxicity between three conditioning regimens were found ($p > 0.05$).

Common adverse effects after AHSCT were as follows: hepatic toxicity (grade 2 and 3) - 20.5%, mucositis (grade 2) - 1.6%, temporary neurological worsening - 6.4%, neutropenic fever - 27%, local infection - 6.2%, anemia (grade 3) - 1.9%, allergic reactions - 2.3%. No differences in toxicity were observed among patients with different conditioning regimens.

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

Quality of life

AHSCT was accompanied by significant improvement in patient's QoL. QoL dramatically improved by all SF-36 scales at 12 months after AHSCT as compared to baseline: PF - 59.59 vs 73.67 ($p < 0.001$), RPF - 45.68 vs 64.24 ($p < 0.001$), BP - 71.38 vs 76.53 ($p = 0.01$), GH - 56.99 vs 69.34 ($p < 0.001$), V - 49.77 vs 64.77 ($p < 0.001$), SF - 66.55 vs 79.55 ($p < 0.001$), REF - 66.04 vs 78.18 ($p = 0.007$), MH - 67.41 vs 74.99 ($p < 0.001$). Improved QoL was preserved during the entire period of follow-up ($p < 0.01$).

QoL profiles in RRMS patients and in SPMS patients at baseline and at 12 months after AHSCT are presented in figure 7, respectively.

As it seen from the figure 7 (a) in patients with RRMS dramatic QoL improvement was observed for all SF-36 scales at 12 months after AHSCT as compared to baseline: PF - 72.5 vs 84.05 ($p < 0.001$), RPF - 52.63 vs 73.08 ($p = 0.001$), BP - 70.13 vs 76.76 ($p = 0.004$), GH - 58.24 vs 72.09 ($p < 0.001$), V - 51.69 vs 66.86 ($p < 0.001$), SF - 68.02 vs 81.41 ($p < 0.001$), REF - 68.44 vs 81.62 ($p = 0.011$), MH - 67.81 vs 76.01 ($p < 0.001$). Improved QoL was preserved during the entire period of follow-up ($p < 0.01$).

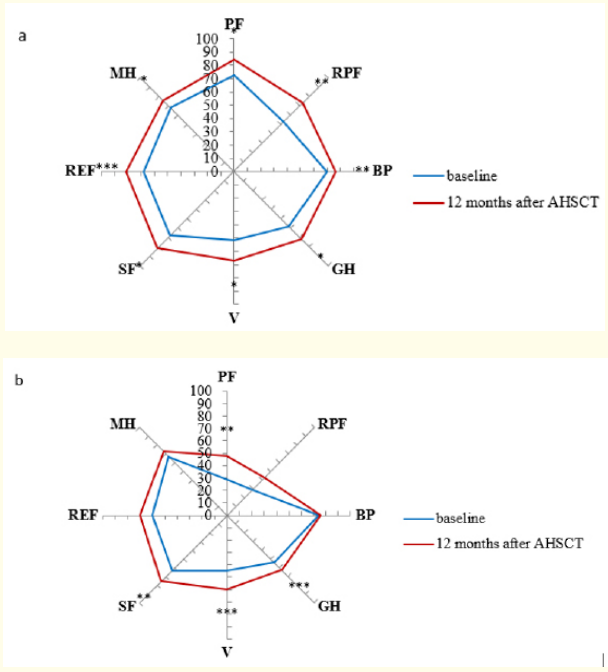

Figure 7: QoL profiles in RRMS (a) and SPMS (b) patients at baseline and 12 months after AHSCT.

Notes: SF-36 Scales - PF: Physical Functioning; RPF: Role Physical Functioning; BP: Bodily Pain; GH: General Health; V: Vitality; SF: Social Functioning; REF: Role Emotional Functioning; MH: Mental Health

*p < 0.001; **p < 0.01; ***p < 0.05.

As for patients with SPMS, significant QoL improvement was revealed for PF - 28.51 vs 47.58 (p = 0.001), GH - 53.95 vs 62.63 (p = 0.02), V - 45.0 vs 59.69 (p = 0.04) and for SF - 62.9 vs 75.0 (p = 0.001), figure 7, b. Improvement for RPF, REF and MH was not significant (RPF - 29.17 vs 42.71 (p = 0.133), REF - 60.22 vs 69.79 (p = 0.334), MH - 66.45 vs 72.50 (p = 0.323); BP was stable during 12 months follow-up period in this patients group.

QoL changes (**Δ**) by SF-36 scales at 12 months after AHSCT and at long-term follow-up after AHSCT (≥ 18 months) as compared to baseline in RRMS patients (a) and SPMS patients (b) are presented in figure 8. As it is seen from the figure QoL further improved by all SF-36 scales after 12 months posttransplant at long-term follow-up in both groups.

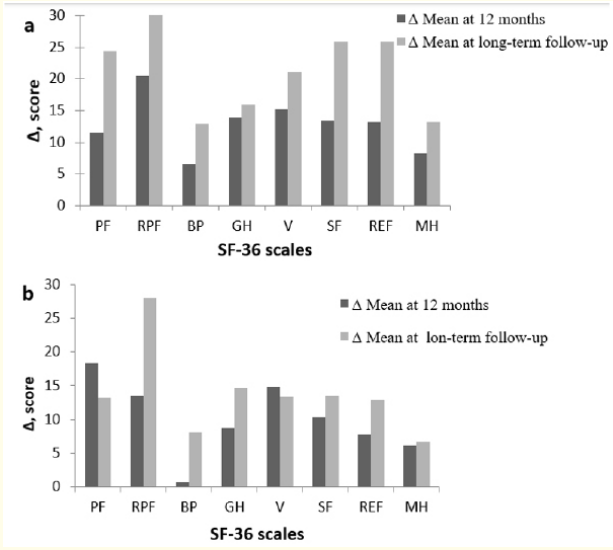

Figure 8: QoL changes in RRMS (a) and SPMS (b) patients at 12 months and at long-term follow-up after AHSCT as compared to baseline.

Notes: SF-36 scales - PF: Physical Functioning; RPF: Role Physical Functioning; BP: Bodily Pain; GH: General Health; V: Vitality; SF: Social Functioning; REF: Role Emotional Functioning; MH: Mental Health

Discussion

The majority of patients with MS have relapsing remitting MS. No current therapy for RRMS can't prevent secondary progressive phase. A large cohort of 418 patients with RRMS and SPMS undergoing HDIT + AHSCT, with a median follow-up of 29.8 months was analysed. Low-intensity conditioning regimens based on BEAM and Cyclophosphamide were applied. Outcomes of AHSCT were evaluated both from physician's and patient's perspective. Good tolerability of transplantation procedure was demonstrated. There were no cases of transplantation-related mortality. In our cohort, response to treatment was achieved in the vast majority of MS patients; all the patients who responded to treatment exhibited clinical improvement or were stable during the entire period of follow-up. Significant decrease of EDSS score was observed after transplantation; the EDSS score improved (decreased by ≥ 1.0 point), with 32% and 17% of patients with RRMS and 32% and

36% in SPMS patients, demonstrating improvement at 2 years and 4 years, respectively. In our cohort, in RRMS patients RFS at 7-year follow-up was 83%. These data are similar to the previously published results by R. Burt [16,17]. In addition, at follow-up of 12 months postransplant, 94.6% patients achieved NEDA-3. As for patients with SPMM, benefits of AHSCT are not so obvious and the data about the use of AHSCT in patients with progressive disease are limited. In a small, open-label study it was shown that five years after transplantation, 42% of patients were stable with no further progression of disability, and it further reduced to 30% 10 years after transplant [39]. No relapses or inflammatory activity was registered on MRI scans after transplantation. These results suggest that AHSCT might be appropriate in a subgroup of SPMS patients that exhibit significant inflammatory activity measured by MRI. In our study which included quite a large cohort of SPMS patients (n = 160) at 12 months after transplantation 85.6% patients achieved NEDA-3; PFS at 7-year follow-up was 77%. These data demonstrate that AHSCT is an effective treatment for MS patients with progressive disease.

Moreover, HDIT + AHSCT resulted in significant improvement in patient's QoL. The analysis of QoL demonstrated benefits of AHSCT with low-intensity conditioning regimens in this patient population. QoL is an important outcome of MS treatment. Evaluation of QoL gives the patient's perspective on the overall effect of treatment and allows to evaluate patient risks/benefits. Our results definitely showed that AHSCT is accompanied with significant and sustained improvement of patient's QoL, both in the groups with relapsing-remitting type and secondary progressive MS.

For the first time to our knowledge in our single-center long-term cohort study, we report outcomes after different conditioning regimens of low intensity in MS patients with different types of the disease. We have shown that no differences in EFS were found between patients who received BM/BEAM-like ± ATG and those who received high-dose Cyclophosphamide + Rituximab. These data are similar to the results we have published previously [28].

Our study also demonstrated that EFS in RRMS was similar in the subgroups of patients with different age and different duration of the disease. On the contrary, disability status was an important factor influencing the outcomes of transplantation: RFS was dramatically better in patients with EDSS < 4 as compared to patients with EDSS ≥ 4 in RRMS patients. This finding supports the idea that AHSCT is beneficial for patients with highly active relapsing remitting RRMS and moderate disability. In SPMM no significant differences in EFS were observed though PFS at 60 months was better in patients of younger age, less disease duration and lower disability status. Further studies are needed to confirm these findings.

This study has several important limitations. First, the study was carried out at a single academic institution, which may introduce the possibility for bias. At the same time, all the patients had clinical continuity and were monitored for in terms of relapses or need for additional treatment. Second, a large number of patients were treated on a compassionate basis, rather than on the study protocol. Third, for a significant proportion of patients long-term follow-up (ie, at ≥ 4 years) was not available. Forth, this is an observational cohort study without a control group, and the results about the benefits of AHSCT can be made with causion.

Thus, the consistency of our clinical results and QoL outcomes, together with the persistence of improvement during the long-term follow-up point to the efficacy of HDIT + AHSCT in MS patients. The results of our study support the feasibility of using reduced-intensity condition regimens. Finally, patients with various types of MS may have benefits after AHSCT with reduced-intensity condition regimens.

Conclusion

The risk/benefit ratio of AHSCT with low-intensity conditioning regimens based on BEAM and Cyclophosphamide in our population of patients with MS is very favorable. Our clinical and QoL results, together with the persistence of improvement are supportive of the efficacy of this AHSCT strategy in MS patients regardless of type of the disease. Overall, the results obtained point to feasibility of AHSCT with low-intensity conditioning in RRMS and SPMS patients. To optimize the treatment protocol of AHSCT with low-intensity conditioning regimens in MS multicenter cooperative studies are needed.

Conflict of Interest

Authors declare no conflict of interest.

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