aHSCT is superior to alemtuzumab in maintaining NEDA and improving cognition in multiple sclerosis

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Abstract

Objective: Autologous hematopoietic stem cell transplantation (aHSCT) is increasingly recognized as a potential therapy for patients with highly active multiple sclerosis (MS). This study aims to assess outcome differences in disease activity in MS patients treated either with aHSCT or alemtuzumab. Methods: We conducted a monocentric registry-based cohort study by recording the clinical course (EDSS and relapses), MRI parameters (new T2 lesions), and neuropsychological assessment in all 19 MS patients receiving aHSCT, and all 21 patients receiving alemtuzumab between 2007 and 2018. We used survival analyses of no evidence of disease activity (NEDA) as the primary objective which was defined by no EDSS progression, no relapse, and no new T2 lesion on MRI. Secondary objectives were EDSS improvement and neurocognitive performance. Results: Both treatment groups were similar in respect of age, gender, disability, and neurocognitive performance except for significantly longer disease duration in the alemtuzumab group. Mean follow-up was 58.8 [range 29–140] months in the aHSCT group compared to 27.6 [range 11–52] months in the alemtuzumab-treated group. We observed significantly more patients maintaining NEDA in the aHSCT group (p = 0.048) compared to the alemtuzumab-treated patients. Furthermore, 37% of the aHSCT patients showed an improvement of EDSS compared to none in the alemtuzumab-treated group (p = 0.033). It is of note that cognitive function was significantly improved in the aHSCT-treated patients. Interpretation: aHSCT suppresses inflammatory activity more effectively than alemtuzumab and might enable improvement of overall disability and cognition in MS.

Introduction

Autologous hematopoietic stem cell transplantation (aHSCT) is increasingly recognized as a potential therapy for multiple sclerosis (MS) patients who are showing high inflammatory activity.1 A recent randomized-controlled trial supports the relevance of aHSCT showing no disease progression in relapsing-remitting MS (RR-MS) in 95% of the patients within the first 2 years after treatment. This is contrasted by only 45% of patients showing no disease progression while they were receiving standard disease-modifying drugs (DMTs).2 Mechanistically, aHSCT holds the promise to eliminate aberrant immune cells and to facilitate a reset of the entire immune system. However, no direct comparison of aHSCT with approved highly effective DMTs has been reported until now. While rates of no evidence of disease activity (NEDA) in the trials that led to the licensing of the individual DMTs were below 60%,3,4 aHSCT-treated patients showed 70–90% NEDA in observational studies.5 Similar to aHSCT, it is thought that alemtuzumab conveys its clinical efficacy by induction therapy; nevertheless, the effectiveness regarding NEDA appears to be inferior to aHSCT. Apart from relapse activity and accumulation of physical disability,
relevant cognitive impairment is frequently observed in MS patients Ref. [6, 7] and contributes crucially to a reduction of daily activity and quality of life. By contrast, there are concerns that aHSCT procedures might also impair cognition based on neurotoxic effects of the procedure.6 Here, we aimed to compare the clinical, radiological, and neuropsychological disease course of MS patients treated with aHSCT following the BEAM-ATG regime to the highly effective DMT alemtuzumab at one center. We hypothesized that aHSCT is superior in maintaining NEDA and preserves cognitive function in high inflammatory MS.

Methods

Study design

This registry-based cohort study followed all 40 patients receiving aHSCT or alemtuzumab between 2007 and 2018 at the University Medical Center Hamburg-Eppendorf, Germany. The treatment decision was based on the clinical judgment of the neurology team. Patients were considered eligible if they had clinically definite MS with high inflammatory activity, that is, recurrent attacks under previous DMTs or rapid clinical progression as defined in working definitions of aggressive disease7 supported by new T2 or gadolinium (Gd)-enhancing MRI lesions. Until the start of the study in 2007, aHSCT in MS had only been performed in few cases in Germany and not yet at our center. Thus, the first transplanted patients were more severely disabled and already in transition to a progressive course, with aHSCT being the only available rescue therapy. With increasing safety experience of aHSCT and growing knowledge about predictors of response, highly inflammatory active patients in earlier disease stages were addressed. After the approval of alemtuzumab in 2013, and until 2016, when aHSCT was put on hold due to missing compensations from insurance companies, decision for either therapy was made in the context of a shared decision-making process that is implemented in the routine clinical care at our center.8,9

We aimed for predetermined annual follow-ups with clinical examination including evaluation of extended disability status scale (EDSS) by an experienced neurologist, neuropsychological assessment, and MRI in both cohorts during their routine visits. An additional short-term follow-up with neuropsychological examination was scheduled 3 months after transplantation for the aHSCT-treated cohort. Safety monitoring was implemented in accordance with the recommendation of the KKNMS (Competence Network Multiple Sclerosis) or EBMT (European Group for Blood and Marrow Transplantation). Early adverse events were systematically assessed in the aHSCT group, but not specifically addressed in the alemtuzumab-treated patients. Longterm side effects were collected by report. To guarantee a continuous and dense data structure as well as for safety reasons, follow-up visits were actively organized by our center and all participants were regularly phoned to schedule next visits. All patients who received alemtuzumab were classified as RR-MS at the time of treatment decision. Since some patients were already in the transition phase, and the disease course often can only be unambiguously assigned in retrospect, two senior neurologists retrospectively reclassified relapsing and secondary progressive MS (SP-MS) based on a review of the clinical documentation if gradual worsening after an initial relapsing course was present.10

All patients provided written informed consent for collection of the data and the use for research purposes. Informed consent for aHSCT or alemtuzumab was obtained as part of the clinical care standard. The monitoring concept of these patient groups has been approved by the local ethics committee (Ärztekammer Hamburg, PV4455).

Primary and secondary endpoints

The primary objective NEDA11 was defined as the absence of relapses, progression, and MRI activity. Relapses were defined as new or worsening neurological symptoms lasting for more than 24 h, progression as 12-month confirmed EDSS increase of ≥1.0 points for EDSS ≤5.0 and ≥0.5 points for EDSS ≥6.0, and MRI activity as new, enlarging, or Gd-enhancing lesions.12 Secondary objectives were 12-month confirmed EDSS improvement, with analogous criteria as for progression, and neurocognitive performance.

Treatment

aHSCT was performed in line with the 2012 guidelines of the EBMT13 according to the Autologous Hematopoietic Stem Cell Transplantation trial in MS (ASTIMS) protocol.14 Briefly, peripheral hematopoietic stem cells (PBSC) were mobilized with 1.5 mg/m² cyclophosphamide over 2 days and on day 2, G-CSF was administered twice daily (total of 5 mg/kg body weight) until the completion of the PBSC harvest. Conditioning regimen was BEAM-ATG (BCNU 300 mg/m² day −7, etoposide 2 × 100 mg/m² day −6 until −3, cytarabine 2 × 100 mg/m² day −6 until −3, melphalan 140 mg/m² day −2, and rabbit anti-thymocyte globulin 3.75 mg/kg body weight days 1 and 2). There was no ex vivo treatment of PBSC. For prophylaxis of infection, fluconazole,
aciclovir, trimethoprim/sulfamethoxazole, and ciprofloxacin were applied. Alemtuzumab was administered in accordance with the guidelines of the KKNMS and approval of the regulatory authorities, that is, 12 mg per day for 5 days at year 1 and 12 mg for 3 days at year 2, as well 2 × 200 mg aciclovir daily for prophylaxis of infection for 4 weeks after infusion.

**Neuropsychological assessment**

A comprehensive battery of standardized neuropsychological tests, covering dimensions mostly affected in MS including attention, processing speed, verbal memory, and executive function, was used to evaluate cognitive performance in different domains. Subtests of the computerized test battery of attention (TAP) were used to assess attention abilities, that is, subtest for phasic and tonic alertness subtest (TAP-PA and TAP-TA), selective attention (TAP-SA), and divided attention subtest (TAP-SA). The Symbol Digit Modalities Test (SDMT) was utilized to measure processing speed.16 To evaluate memory and learning abilities, we administered the Verbal Learning and Memory Test (VLMT),17 the German version of the auditory-verbal learning test. To quantify executive functions, we used the Regensburg Verbal Fluency Test (RWT), specifically subtest letters G-R to assess verbal cognitive flexibility,19 and the Trail Making Test Form B (TMT-B)20 to evaluate task switching abilities. For most of the tests, parallel version was used to minimize learning effects. Results were normalized for age and education and results are displayed with corresponding T-scores (T), z-scores (z), or percentage ranks (PR), respectively.

**Statistical analyses**

Besides providing descriptive statistics for the two groups, we compared baseline characteristics between the cohorts by Chi-square or Student’s t-testing depending on the nature of the data. For NEDA and EDSS improvement analyses as well as the individual NEDA components, we used Cox proportional hazard models and log-rank test to compare time-to-event differences between groups. Analysis of EDSS progression compared EDSS deterioration to EDSS stabilization or EDSS improvement, whereas analysis of EDSS improvement compared EDSS improvement to EDSS stabilization or deterioration. The change in cognitive performance over time was compared by ANOVA of linear mixed effect models adjusted for disease duration allowing random intercepts and divergent follow-up times. p values below 0.05 were considered statistically significant. Analysis was conducted using R 3.5.2 Software.

**Data availability statement**

Data are available upon reasonable request by interested researchers.

**Results**

**Patient characteristics**

Demographic and clinical data are displayed in Table 1. Nineteen patients received aHSCT and 21 were treated with alemtuzumab—detailed information about the individual patients and inclusion criteria are displayed in Table 2. Seven patients in the aHSCT cohort suffered from a progressive disease course compared to five in the alemtuzumab group. There were no significant differences regarding sex, age, EDSS, or number of prior exacerbations regarding sex, age, EDSS, or number of prior exacerbations.

| Table 1. Baseline characteristics from the aHSCT and alemtuzumab cohort. |
|-----------------------------------------------|------------------|------------------|
| Age years (SD)                              | aHSCT (n = 19)   | Alemtuzumab (n = 21) |
| Female n (%)                                | 12 (63.2)        | 14 (66.7)         |
| Disease duration years (SD)                 | 5.4 (4.2)        | 11.3 (6.8)        |
| Disease course n (%) RRMS                   | 12 (63.1)        | 16 (76.2)         |
| PPMS                                         | 3 (15.8)         |                  |
| SPMS                                         | 4 (21.1)         | 5 (23.8)          |
| Prior Immunotherapies (SD)                  | 2.37 (1.21)      | 2.76 (1.51)       |
| Relapse within past 2 years n (SD)          | 1.79 (1.98)      | 1.38 (1.12)       |
| Last relapse month (SD)                     | 9.4 (7.6)        | 8.2 (9.0)         |
| Follow-up years (range)                     | 4.9 [29–149]     | 2.3 [11–52]       |

**Disability and cognition at baseline**

| EDSS median [IQR]                            | aHSCT (n = 19)   | Alemtuzumab (n = 21) |
|-----------------------------------------------|------------------|---------------------|
| TAP PA T median [IQR]                         | 38 [8]           | 44 [10]             |
| TAP TA T mean [range]                         | 40 [10.5]        | 46.5 [11.3]         |
| TAP SA T mean [range]                         | 37 [12.5]        | 39 [12.5]           |
| TAP DA T mean [range]                         | 43 [13]          | 45 [13]             |
| SDMT z mean [range]                           | -0.1 [2.1]       | 0 [2.2]             |
| TMT-B z PR [range]                            | 35 [68.8]        | 9 [46.5]            |
| RWT-GR PR mean [range]                        | 11 [22]          | 20 [35]             |
| VLMT 1–5 mean [range]                         | -0.3 [1.6]       | 0.5 [1.9]           |
| VLMT 5–7 mean [range]                         | 0.2 [2.4]        | 0.2 [1.3]           |

**Bold = significant differences.**

1 Only RRMS patients included.
2 Student’s t-test.
3 Chi-squared test.

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Table 2. Individual patient characteristic and specification of disease status before therapy initiation.

| Patient No. | Therapy | Sex | Disease | Disease Course | Prior Therapies | Disease Duration<sup>1</sup> | Age<sup>1</sup> | Baseline EDSS | Attack 2 year prior therapy | Last Attack | MRI activity<sup>2</sup> 1 year prior therapy |
|-------------|---------|-----|---------|----------------|-----------------|-----------------------------|--------------|---------------|----------------------------------|-------------|---------------------------------|
| 1           | aHSCT   | Female | SPMS    |                | GLAT, MITOX, DAC, CYC | 16             | 39            | 6.5           | 2                                | >12 month   | no                             |
| 2           | aHSCT   | Female | SPMS    |                | IFN, MITOX       | 7              | 32            | 6.0           | 0                                | >12 month   | no                             |
| 3           | aHSCT   | Female | SPMS    |                | IFN, GLAT, MITOX | 9              | 45            | 7.0           | 0                                | >12 month   | no                             |
| 4           | aHSCT   | Female | SPMS    |                | IFN, AZA, MITOX  | 7              | 47            | 6.5           | 0                                | >12 month   | no                             |
| 5           | aHSCT   | Male   | RRMS    |                | IFN              | 1              | 31            | 2.0           | 6                                | 8           | yes                            |
| 6           | aHSCT   | Female | RRMS    |                | IFN, NAT         | 5              | 23            | 0.0           | 2                                | 5           | yes                            |
| 7           | aHSCT   | Female | RRMS    |                | IFN, NAT         | 1              | 43            | 5.5           | 3                                | 1           | na<sup>3</sup>                   |
| 8           | aHSCT   | Female | RRMS    |                | IFN, GLAT, NAT   | 6              | 29            | 4.0           | 1                                | 9           | yes                            |
| 9           | aHSCT   | Female | RRMS    |                | IFN, GLAT, NAT   | 4              | 50            | 6.0           | 6                                | 1           | yes                            |
| 10          | aHSCT   | Female | RRMS    |                | IFN, NAT, FTY    | 9              | 26            | 5.5           | 0                                | >12 month   | yes                            |
| 11          | aHSCT   | Male   | PPMS    |                | none             | 1              | 29            | 3.5           | 0                                | na<sup>3</sup> | yes                            |
| 12          | aHSCT   | Male   | PPMS    |                | IFN              | 1              | 37            | 3.5           | 1                                | >12 month   | yes                            |
| 13          | aHSCT   | Male   | RRMS    |                | IFN, FTY, NAT    | 5              | 42            | 6.0           | 1                                | >12 month   | no                             |
| 14          | aHSCT   | Female | RRMS    |                | GLAT, NAT        | 4              | 19            | 3.0           | 2                                | >12 month   | yes                            |
| 15          | aHSCT   | Female | RRMS    |                | IFN, NAT, GLAT, FTY, NAT | 12 | 32 | 6.5 | 4 | 1 | yes |
| 16          | aHSCT   | Female | RRMS    |                | IFN, NAT         | 1              | 21            | 2.5           | 4                                | 6           | yes                            |
| 17          | aHSCT   | Male   | RRMS    |                | IFN, FTY, NAT    | 4              | 31            | 2.0           | 2                                | 8           | no                             |
| 18          | aHSCT   | Male   | PPMS    |                | RTX              | 1              | 55            | 6.0           | 0                                | na<sup>3</sup> | no                             |
| 19          | aHSCT   | Male   | RRMS    |                | IFN, NAT, FTY    | 9              | 35            | 4.0           | 0                                | >12 month   | no                             |
| 20          | Alemtuzumab | Male | RRMS    |                | IFN, NAT, FTY    | 11             | 32            | 6.0           | 0                                | >12 month   | yes                            |
| 21          | Alemtuzumab | Female | RRMS   |                | IFN, GLAT, FTY, NAT | 2 | 25 | 5.0 | 2 | 5 | yes |
| 22          | Alemtuzumab | Female | RRMS   |                | FTY, IFN, TFM    | 7              | 52            | 3.5           | 1                                | 5           | yes                            |
| 23          | Alemtuzumab | Female | RRMS   |                | IFN, MITOX, DAC  | 11             | 31            | 7.0           | 3                                | 4           | na<sup>3</sup>                   |
| 24          | Alemtuzumab | Female | RRMS   |                | IFN, NAT         | 8              | 25            | 3.0           | 1                                | 2           | yes                            |
| 25          | Alemtuzumab | Female | RRMS   |                | IFN, NAT, FTY, DAC | 16 | 58 | 6.0 | 2 | 1 | yes |
| 26          | Alemtuzumab | Female | RRMS   |                | IFN, FTY        | 24             | 46            | 6.0           | 3                                | 4           | na                             |
| 27          | Alemtuzumab | Female | RRMS   |                | IFN, NAT, FTY    | 8              | 36            | 3.0           | 1                                | 9           | yes                            |
| 28          | Alemtuzumab | Female | RRMS   |                | GLAT, NAT, IFN, DMF | 10 | 38 | 2.0 | 3 | 4 | yes |
| 29<sup>4</sup> | Alemtuzumab | Female | RRMS   |                | IFN, DMF, FTY, NAT | 18 | 34 | 4.0 | 0 | >12 month | no |
| 30          | Alemtuzumab | Female | RRMS   |                | IFN, DMF        | 4              | 35            | 5.5           | 0                                | >12 month   | yes                            |
| 31          | Alemtuzumab | Male   | SPMS    |                | IFN, DMF        | 10             | 46            | 5.5           | 1                                | 5           | yes                            |
| 32          | Alemtuzumab | Female | RRMS   |                | none            | 1              | 24            | 1.0           | 1                                | 1           | yes                            |
| 33          | Alemtuzumab | Female | RRMS   |                | IFN, NAT, DMF   | 11             | 50            | 5.5           | 2                                | 7           | yes                            |
| 34          | Alemtuzumab | Female | RRMS   |                | TFM             | 10             | 41            | 4.0           | 1                                | 9           | yes                            |
| 35          | Alemtuzumab | Female | RRMS   |                | AZA, IFN        | 25             | 47            | 4.0           | 1                                | 1           | yes                            |
| 36          | Alemtuzumab | Male   | RRMS    |                | IFN              | 17             | 40            | 5.0           | 1                                | 4           | yes                            |
| 37          | Alemtuzumab | Male   | SPMS    |                | IFN, MITOX      | 15             | 39            | 6.0           | 1                                | 1           | no                             |
| 38          | Alemtuzumab | Male   | RRMS    |                | IFN, GLAT, FTY  | 19             | 41            | 7.0           | 1                                | >12 month   | no                             |

<sup>1</sup>Duration of disease in years prior to therapy initiation; Age at therapy initiation; Baseline EDSS: disability status at therapy initiation; Last Attack: time of last documented disease activity;  MRI activity: presence of MRI activity prior to therapy initiation.

<sup>2</sup>MRI activity: presence or absence of MRI activity prior to therapy initiation.

<sup>3</sup>na: Not applicable.

<sup>4</sup>Continued

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immunotherapies at baseline. Disease duration, however, was significantly longer in the alemtuzumab-treated patients (mean (SD) 11.3 (6.8) years vs. aHSCT 5.4 (4.2), \( p = 0.002 \)). Follow-up was 58.8 (SD 36.0) months in the aHSCT group compared to 27.6 (SD 14.4) months in the alemtuzumab-treated patients. All patients showed ongoing inflammatory activity, that is, recurrent attacks, new or Gd-enhancing lesions, or rapid progression in the year before treatment initiation. All RR-MS patients had at least one relapse in the past 24 months. However, the number of relapses in the past 2 years tended to be higher in the aHSCT group (mean (SD) 1.8 (2.0) vs. alemtuzumab 1.4 (1.12), \( p = 0.225 \)), whereas the time interval to the last attack did not differ between groups.

**aHSCT increases the persistence of NEDA by suppressing inflammatory activity**

62.0% (95% CI 47.2–92.2) of the aHSCT-treated patients showed NEDA at the end of the observation period, compared to 40.2% (95% CI 16.3–99.0) in the alemtuzumab group (\( p = 0.038 \)) (Fig. 1). Failure to maintain NEDA was due to inflammatory activity as measured by new T2 lesions or relapses. Within 5.4 years (mean) of follow-up, we observed no signs of inflammatory activity, that is, MRI activity or relapses, in the aHSCT group. In the alemtuzumab cohort, only 48.9% showed no new T2 lesions (95% CI 20.7–100.0, \( p = 0.001 \)) and 87.3% had no relapses (95% CI 71.8–100.0, \( p = 0.120 \)). Notably, seven patients (35.7%, 95% CI 15.5–82.4) of the aHSCT-treated group experienced 12-month confirmed EDSS improvement, whereas none of the alemtuzumab-treated patients showed improvements in their EDSS score (\( p = 0.033 \)). EDSS progression was similar in both groups. None of the patients in the aHSCT group received additional immunotherapy after transplantation, whereas two patients in the alemtuzumab group were switched to ocrelizumab after 24 months.

**aHSCT but not alemtuzumab counteracts cognitive decline**

At baseline, patients of both treatment groups showed an MS typical performance profile in several cognitive domains (Table 1). There were no significant differences between baseline neurocognitive function, except for inferior performance in tonic alertness in the aHSCT group (\( p = 0.049 \)). Notably, patients receiving aHSCT showed improved cognitive function in contrast to patients treated with alemtuzumab during the follow-up. Compared to the aHSCT group, age- and education-adjusted \( T \)-values of the alemtuzumab-treated patients deteriorated annually by 2.10, 2.47, 2.55, and 2.25, respectively, for phasic alertness, tonic alertness, selective alertness, and divided attention (Fig. 2). Similarly, performance for attention processing and cognitive flexibility decreased by 0.13 and 1.55 \( z \)-scores or percentiles per year, respectively. Only minor effects were observed for verbal learning (0.07), verbal memory (0.02), and task switching (0.89), which corresponded to a superior performance of the aHSCT-treated patients in six of nine tests. These effects were most pronounced and significantly altered in the domains of attention and information processing, that is, phasic alertness, tonic alertness, selective alertness, and divided attention (Fig. 2). None of the aHSCT-treated patients’ cognitive performance worsened in the short term (3 months) or in the long term after treatment. Alemtuzumab-treated patients deteriorated in all tested domains.

| Patient | Therapy | Sex | Disease Course | Prior Therapies | Disease Duration | Age | Baseline EDSS | Attack 2 year prior therapy | Last Attack | MRI activity |
|---------|---------|-----|----------------|-----------------|-----------------|-----|---------------|----------------------------|-------------|--------------|
| 39      | Alemtuzumab | Male | SPMS           | IFN, RTX, DMF, TFM | 10              | 36  | 6.5           | 0                           | >12 month   | Yes          |
| 40      | Alemtuzumab | Male | RRMS           | DMF             | 1               | 21  | 3.0           | 4                           | 1           | Yes          |

Abbreviations: aHSCT, autologous hematopoietic stem cell transplantation; SPMS, secondary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; GLAT, glatiramer acetate; MITOX, Mitoxantrone; DAC, Daclizumab; CYC, Cyclophosphamide; IFN, Interferons; AZA, Azathioprine; NAT, Natalizumab; FYI, Fingolimod; RTX, Rituximab; DMF, dimethyl fumarate; TFM, teriflunomide; na, not available.

1At time point of therapy.

2New lesions or gadolinium enhancement.

3No MRI feasible because of permanent pacemaker or deep brain stimulation, respectively.

4Switched from NAT because of positive JCV titer.

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Figure 1. Disability progression and inflammatory activity. Kaplan–Meier curve for NEDA (A), single NEDA elements (B), and EDSS improvement (C). Time-to-event differences between the aHSCT-treated and alemtuzumab-treated patients were calculated by Cox proportional hazard models.
Neuropsychological assessment: changes in neurocognitive performance were compared by ANOVA of linear mixed effect models adjusted for disease duration. Results were normalized for age and education and the space between the dotted lines shows standardized norm values calculated with corresponding T-score for the single TAP items (test battery for attentional performance), with z-score for SDMT (symbol digit modalities test) and VLMT (verbal learning and memory task) and with percentile rank for TMT-B (trial making test B) and RWT-GR (Regensburger word fluency task, respectively). TAP was implemented to evaluate attention, and information processing was assessed by SDMT and TMT-B. Supraspan and verbal learning as well as memory were measured by the VLMT, and cognitive flexibility was assessed by RWT-GR. The normal values for T-scores are 40–60, –1 to 1 for z-scores, and 16–84 for percentiles. p values correspond to group \times time interaction.
aHSCT shows a reasonable safety profile

Early adverse events in the aHSCT-treated group are displayed in Table 3 and correspond to the expected side effects. With regard to long-term side effects, one death due to BCR/ABL-positive chronic myeloid leukemia occurred 4 years after therapy in the aHSCT-treated group, which was associated with an earlier therapy of mitoxantrone.21,22 One aHSCT-associated polyarthritis was observed, but resolved after a single dose of rituximab. Furthermore, one case of autoimmune thyroid disease occurred as well as a case of infertility in a 20-year-old woman. In the alemtuzumab group, three cases of autoimmune thyroid disease were observed, as well as two patients with severe idiopathic thrombocytopenic purpura (ITP) and one with alopecia areata. All cases of thyroid disease required substitution of thyroid hormones and one required a thyroidectomy. ITP was successfully treated with steroids.

Discussion

aHSCT is increasingly recognized as a potential therapy for MS patients, but it is still not firmly established and its efficacy compared to highly effective DMTs has hardly been studied. Based on the results of our study, aHSCT seems to be even more effective than second-line DMTs, which have so far shown the most promising results in terms of effectiveness in reducing relapse rates and the evolution of new or enlarging lesions. In line with available data,2,14,21 our study further builds on existing evidence that aHSCT effectively reduces inflammatory activity in terms of relapses and new T2 lesions. Failure to maintain NEDA in the aHSCT-treated patients was mostly due to disability progression which was primarily observed in patients with progressive disease, whereas MRI activity and relapses were completely suppressed. However, in the alemtuzumab-treated group, new T2 lesions as well as relapses were frequently observed, despite longer disease duration and lower pre-study relapse activity. Although we cannot directly conclude this from our data, we assume that both factors lower the risk for on-trial disease activity in the alemtuzumab group.

Going beyond previous studies,22 it is remarkable that we did not only observe a significant proportion of aHSCT patients remaining NEDA, but also noticed a substantial number of patients with improved disability as measured by a 12-months confirmed lower EDSS score, as well as improved cognitive function, despite more patients in the aHSCT group with a progressive course who had less overall evidence of inflammatory activity. The effects on cognition were detectable despite concerns about aHSCT-associated neurotoxicity of chemotherapy and the already existing deficits prior to therapy. A previously discussed neurotoxicity of the BEAM-ATG regime23,24 with impact on cognition seems very unlikely based on our findings. None of the approved DMTs have yet convincingly shown to enable disability improvement or improved cognitive performance. It is not likely that these effects are mediated through the transplantation process. Neither aHSCT nor alemtuzumab directly enable regeneration of the CNS while they profoundly alter the immune system which results in dampened inflammatory activity. Although inflammation is known to be multifaceted in the context of regeneration in MS and may also contribute to repair,25 it is conceivable that effectively eradicating autoreactive immune cells and thereby interrupting harmful pathways might facilitate endogenous repair processes.26 However, secondary neuroregeneration based on anti-inflammatory treatments is poorly understood. Along the same line, it is not even clearly known how HSCT mediates its effects, although immunosuppression induced by the conditioning regimen is most likely the main mechanism.

This study has several limitations, as we included only few patients, no randomization was performed and data were collected along regular clinical visits. The study was observational, evolving with aHSCT experience as well as

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**Table 3. Early adverse events in the aHSCT cohort.**

| Patient | Adverse event |
|---------|---------------|
| 1       | Pneumogenic sepsis (HSV), GI toxicity grade 1, mucositis grade 2 |
| 2       | Urosepsis (E. coli), urticaria |
| 3       | Liver toxicity grade 1, mucositis grade 2 |
| 4       | FUO, CVC infection |
| 5       | none |
| 6       | FUO |
| 7       | FUO, pneumonia (Aspergillus), CVC infection (Staph. epidermidis), mucositis grade 2 |
| 8       | Stomatitis (HSV) |
| 9       | FUO, UTI (Staph. hemolyticus) |
| 10      | FUO, UTI, tonsillitis |
| 11      | FUO, exanthema |
| 12      | FUO |
| 13      | FUO |
| 14      | CVC infection, dermatomycosis, noroviral colitis, mucositis grade 2 |
| 15      | Sepsis |
| 16      | FUO, UTI (E. coli), mucositis grade 2 |
| 17      | FUO, mucositis grade 2 |
| 18      | FUO, oral candidiasis, tachyarrhythmia absoluta |
| 19      | Pneumogenic sepsis (HSV), GI toxicity grade mucositis grade 1, mucositis grade 2 |

Abbreviations: GI, gastrointestinal; FUO, fever of unknown origin; CVC, central venous catheter; HSV, Herpes simplex virus; UTI, urinary tract infection.

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new treatment approvals since alemtuzumab was only available 6 years after the first transplant. These factors might influence the study results leading to selection and detection bias. Nevertheless, only 16 of the 40 patients participating in the study were recruited in the period when both therapies were available and those patients were offered both forms of therapy. Additionally, relapses cannot always be assessed objectively and the EDSS is known to have a poor inter-rater validity. As such, both have considerable weaknesses as outcome parameters. Furthermore, it is known that cognitive performance has high intraindividual variability in patients with impaired neurological function, and cognitive performance of MS patients can, among others, vary according to temperature or mood. Although our data are quite heterogeneous and should be interpreted with caution, the overall cognitive profile still gives a signal toward improved cognitive function and contradicts the neurotoxic effect of the aHSCT procedure. Moreover, MRI is known to be highly reproducible and we therefore believe that the homogenous clinical, neuropsychological, and MRI results support the validity of our findings. Furthermore, alemtuzumab-treated patients had a 5-year longer disease duration at baseline, which might be discussed as another confounder. A longer disease duration, however, is generally associated with less focal inflammatory activity. NEDA failure due to clinical progression in turn did not differ between groups, but relapses as well as new T2 lesions were significantly more frequent in the alemtuzumab group. The shorter follow-up period in the alemtuzumab cohort could have also biased the study results. However, due to the long observation period in the aHSCT group, we would have expected the risk of relapse and progression to be higher than in a cohort with a shorter observation period, but our results suggest the opposite. Despite this censoring in favor of alemtuzumab, the performance of alemtuzumab was worse. Finally, we were not able to compare subgroups due to the small sample size, even though this would clarify the impact of different disease course on the outcome after aHSCT or alemtuzumab, respectively.

In summary, aHSCT appears highly effective in suppressing inflammatory activity, making it a promising as well as safe therapeutic approach for MS patients with highly active disease. Remarkably, aHSCT might even facilitate improvement of disability and cognition in patients with a high risk for fast disability accumulation. Our findings support the higher efficacy in relapsing-remitting MS compared to more neurodegenerative progressive MS. Further research and randomized controlled trials comparing aHSCT to second-line DMTs are warranted and required to establish aHSCT within the treatment landscape of MS.

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Author Contribution
VH: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content. FU: Interpreted the data; revised the manuscript for intellectual content. JP: Major role in the acquisition of data. CW: Interpreted the data; revised the manuscript for intellectual content. MAF: Interpreted the data; revised the manuscript for intellectual content. NK: Interpreted the data; revised the manuscript for intellectual content. CH: Design and conceptualized study; interpreted the data; revised the manuscript for intellectual content. JPS: Design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.

Conflict of Interest
Vivien Häußler has nothing to disclose. Friederike Ufer has nothing to disclose. Jana Pöttgen received research funding from Hertie Foundation, Deutsche Rentenversicherung Bund and Bayer outside the submitted work. Christine Wolschke has nothing to disclose. Manuel A. Friese reports research funding from Deutsche Forschungsgemeinschaft, BMBF and Hertie Foundation without connection to the submitted work. Nicolaus Kröger received a research grant from Neovii. Christoph Heesen received speaker honoraria and research grants from Genzyme, Merck, Novartis, and Roche. Jan-Patrick Stellmann reports personal fees from Biogen, Genzyme, and Alexion and received research funding from Deutsche Forschungsgemeinschaft, BMBF, and Genzyme outside the submitted work.

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