Autologous hematopoietic cell transplantation following high-dose immunosuppressive therapy for advanced multiple sclerosis: long-term results

James D. Bowen, MD[1], **George H. Kraft, MD, MS**[2], **Annette Wundes, MD**[3], **QingYan Guan, MS**[4], **Kenneth R. Maravilla, MD**[4], **Theodore A. Gooley, PhD**[5,6], **Peter A. McSweeney, MD**[7], **Steven Z. Pavletic, MD**[8], **Harry Openshaw, MD**[9], **Rainer Storb, MD**[5,6], **Mark Wener, MD**[2], **Bernadette A. McLaughlin, RN**[6], **Gretchen R. Henstorf, CCRC**[6], and **Richard A. Nash, MD**[5,6]

[1]Swedish Neuroscience Institute, Seattle, WA; University of Washington, Seattle, WA

[2]Department of Rehabilitation Medicine, Seattle, WA

[3]Department of Neurology, Seattle, WA

[4]Department of Radiology, Seattle, WA

[5]Department of Medicine, Seattle, WA

[6]Fred Hutchinson Cancer Research Center, Seattle, WA

[7]Colorado Blood and Cancer Institute, Denver, CO

[8]National Cancer Institute, Bethesda, MD

[9]City of Hope, Duarte, CA

Abstract

The purpose of the study was to determine the long-term safety and effectiveness of high-dose immunosuppressive therapy (HDIT) followed by autologous hematopoietic cell transplantation (AHCT) in advanced multiple sclerosis (MS). Total body irradiation, cyclophosphamide, and antithymocyte globulin were followed by transplantation of autologous, CD34-selected peripheral blood stem cells (PBSC). Neurological examinations, brain MRIs and cerebrospinal fluid (CSF) for oligoclonal bands (OCB) were serially evaluated. Patients (n=26, mean EDSS=7.0, 17 secondary progressive, 8 primary progressive, 1 relapsing/remitting) were followed for a median of 48 months after HDIT followed by AHCT. The 72-month probability of worsening ≥ 1.0 EDSS point was 0.52 (95% CI, 0.30 to 0.75). Five patients had an EDSS at baseline of ≥ 6.0; four of these had not failed treatment at last study visit. OCB in CSF persisted with minor changes in the banding pattern. Four new or enhancing lesions were seen on MRI, all within 13 months of treatment. In this population with high baseline EDSS, a significant proportion of patients with advanced MS remained stable as long as 7 years after transplant. Non-inflammatory events may

Corresponding Author: Richard A. Nash, MD, D1-100 Clinical Research Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, PO Box 19024, Seattle, WA 98109, Phone: 206-320-2200, Fax: 206-667-4978, rnash@fhcrc.org.

have contributed to neurological worsening after treatment. HDIT/AHCT may be more effective in patients with less advanced relapsing/remitting MS.

Keywords

multiple sclerosis; total body irradiation; cyclophosphamide; hematopoietic cell transplantation; oligoclonal bands

Introduction

Inflammation of the central nervous system (CNS) is a prominent feature of multiple sclerosis (MS). This is most notable in acute lesions where inflammation plays a role in the breakdown of the blood-brain-barrier, migration of immunocytes into the CNS, and production of pro-inflammatory cytokines and neuronal damage. While inflammation is most severe in acute MS lesions, it is also found in other areas of the brain and spinal cord, including the cortex. Though the role of inflammation has most often been studied in relapsing/remitting MS (RRMS), it is present and also likely plays a role in the progressive forms of the disease.[1] Medications currently approved by the FDA are only partially effective for slowing progression or reducing the number of relapses and not effective for progressive MS.[2] More effective treatments are clearly needed.

In animal models, autoimmune inflammatory demyelination is controlled by high-dose immunosuppressive regimens, including those that require rescue with autologous hematopoietic cell transplantation (AHCT).[3] A significant proportion of patients with other immune-mediated diseases have had durable responses to high-dose immunosuppressive therapy (HDIT) followed by AHCT.[4–7] In preclinical studies of high-dose immunosuppressive regimens for autoimmune diseases, total body irradiation (TBI) was a more effective immunosuppressive treatment than chemotherapeutic regimens, so TBI was included in the HDIT regimen for this study.[8] We had published our initial findings previously and now report the long-term outcomes.[9]

Patients and Methods

Study design and patients

The study design and the safety and response outcomes of this study have been reported previously.[9,10] Data for the long-term follow-up analysis was collected from 2005 through 2008. The study was approved by the Institutional Review Boards at the participating sites. The ClinicalTrials.gov identifier is NCT00014755.

Eligible patients had clinically definite or laboratory-supported definite MS by Poser criteria[11] and a primary progressive (PP), secondary progressive (SP), or relapsing/remitting (RR) course.[12] Patients with RRMS required two or more attacks in the previous two years, and all patients had to have a worsening in the Expanded Disability Status Scale (EDSS)[13] of 1.0 or more points over the preceding year. Baseline EDSS of 5.0 to 8.0 at entry into the study was required. Patients were excluded if they had co-morbidities that precluded the safe use of HDIT.

Procedures

PBSC were mobilized with rhG-CSF (16 μg/kg/day), collected, and then CD34-selected by an Isolex 300I column (Baxter, Deerfield, IL).[14] A minimum of 3.5×10^6 CD34+ cells/kg were required for HCT. Because of an MS exacerbation during mobilization in the fourth patient, subsequent patients were treated with prednisone 1 mg/kg/day for 10 days.

Immunosuppressive treatment included fractionated total body irradiation (800 cGy), cyclophosphamide (Cy) 120 mg/kg and equine antithymocyte globulin (ATG; ATGAM; Pharmacia, Peapack, NJ) 90 mg/kg. The transplant regimen and posttransplant supportive care has been previously described.[9]

Outcome measures

Scheduled clinical evaluations were performed before stem cell mobilization (baseline) and at months +1, +3, +12 and +24 as previously described.[9] Patients returned for further evaluations and MRI scans of the brain between 3–7 years after transplant. The time of EDSS failure was the first of two consecutive measures or the last study visit at which the EDSS was increased 1 point. The number of exacerbations after day 0 of transplant was recorded.

Cerebrospinal fluid (CSF) examination was performed at baseline and at +3, +12 and +24 months. The results from the clinical testing of CSF for oligoclonal bands (OCB) at the participating sites had been previously reported.[9] Since these results were based on reports from different hospital laboratories at the collaborating sites, all the available CSF and serum samples from baseline to 2 years after transplant were studied again by isoelectric focusing (IEF) in a central laboratory at the University of Ottawa.[15] CSF samples were later collected from patients 3 and 24 at +4 and +6 years as part of the long-term follow-up and tested at the University of Washington. Oligoclonal banding tests were performed with the Sebia Hydragel CSF IEF system (Sebia, Inc, Norcross, GA), using IgG-specific antibody reagents and methods recommended by the manufacturer. CSF and serum specimens were diluted to achieve a similar concentration of IgG before loading on the IEF gels. Laboratory personnel were unaware of the chronological order of the CSF specimens for interpreting the results.

Brain magnetic resonance imaging (MRI) scans were performed at the scheduled study visits. The scans were reviewed by a single blinded neuroradiologist who qualitatively assessed scans for new or expanding T2-weighted lesions and new gadolinium-enhancing lesions. Each patient's scans were displayed with the dates masked and the chronological order randomized. A subset of brain MRI scans of patients treated in Seattle was additionally analyzed to quantify T2 lesion volume and total brain volume. These MRI scans utilized 3-mm slice thickness, no interslice gap, and reproducible positioning. The iQuantify program (Insightful Corp., Seattle, WA) was used to quantify T2 lesion burden and brain volume.

Statistics

Safety and efficacy endpoints were reported in a descriptive analysis based on the last follow-up of each patient. Overall survival was estimated using the method of Kaplan and Meier, and disease progression was summarized using a cumulative incidence estimate.[16,17] Linear regression was used to estimate the linear change in EDSS with respect to time posttransplant. Generalized estimating equations were used to estimate the confidence interval for change in EDSS. Change in brain and lesion volume was assessed using a one-sample t-test.

Results

Patient characteristics

Of the 26 patients enrolled, 12 were female. Most had SPMS ($n = 17$) or PPMS ($n = 8$) disease with a single case of RRMS. The median age at entry was 41 (range 27–60) years. The median disease duration at entry was 84 (range 10–277) months. The median EDSS was 7.0 (range 5.0–8.0). Patients were followed for a median of 48 (range 3–72) months.

In the original report of this study, two patients had died and two patients were unwilling or unable to return to the study center for neurological evaluation.[9] In the follow-up phase, one additional patient died before another study evaluation was done, and three patients were unable or unwilling to travel for an evaluation by the study neurologist. Two of these patients had already met the EDSS-failure endpoint. Additional data on the neurological status (n=18) and survival (n=2) was obtained for 20 patients.[9]

Evaluation of disease

Clinical assessment of neurological function—Comparing the EDSS at baseline and last study visit, disability was worse by   1.0 EDSS point in 10 of 26 patients (38%) and improved in 4 (0.5 point) (Table 1). Disability was worse in 15 patients by   0.5 EDSS points. EDSS failure or worsening was defined as an increase in the EDSS by   1 point on any two consecutive measures or at last study visit. The estimated probability of worsening at 72 months was 0.52 (95% CI, 0.30 to 0.75) (Figure 1). Median time to EDSS failure for the 11 patients was 3.0 (0.5–5.0) years. At 72 months, the estimated probability of an increase in EDSS by   0.5 points on any two consecutive measures among those patients with a baseline EDSS above 5.0, was 65% (95% CI, 0.43–0.87).

Five patients had an EDSS at baseline of   6.0. Four of these 5 patients had not failed treatment at last study visit. Five of the 8 patients with PPMS had not failed treatment at last study visit, but two of these patients did not have a follow-up beyond 1 year. The only patient with RRMS remained neurologically stable at +6 years even though the baseline EDSS was 7.0.

A single clinical relapse occurred shortly after transplant during an engraftment syndrome. No other clinical relapses were observed. No subject was put back on a disease-modifying treatment. Of 23 evaluable patients, 7 patients had gadolinium-enhancing lesions at baseline and 3 (43%) had evidence of progression (EDSS   1.0 point). This was similar to that

observed in 16 patients without gadolinium-enhancing lesions of whom 8 (50%) had progression.

Assessment of brain MRI—As previously reported, new, enhancing MRI lesions were noted in four patients all within 13 months of treatment. Among the subset of patients being followed in Seattle, the estimated mean decrease in T2 lesion volume from baseline to 2 years among patients with MRI scans at each of these times (n=9) was 2.7% (S.D.=19.3%, p=0.69). The mean decrease in T2 lesion volume from +2 to +5 years among 8 patients with measurements at each time was −12.3% (S.D.=39.1%, p=0.40). The estimated mean decrease in brain volume from baseline to +2 years (change expressed as the mean of the differences between baseline and 2 years; n=12) was 2.6% (S.D.= 2.9%, p=0.01). Nine of these patients also had MRI scans at +5 years. The mean decrease in brain volume from +2 to +5 years was 4.4% (S.D.=5.9%, p=.06). While the sample size was small, these data do not suggest that the accelerated rate in brain volume loss observed early after transplant decreases after 2 years in patients with advanced MS.

Assessment of CSF—CSF was available at baseline and follow-up in 15 patients. Post-transplant samples were obtained at a median of +12 months (range 3–72). Comparing OCB at baseline and follow-up at +12 or +24 months, the same bands were present in 12 specimens. Two had a decreased number of bands (one from 11 to 6, and one from 14 to 11). One had no bands at baseline, but three bands at follow-up. Patients 3 and 24 had OCB studies done as part of the long-term follow-up study at +48 and +72 months (Figure 2). OCB persisted in both patients but there was attenuation of some of the bands at these late time points.

Long-term complications and survival—The short-term complications were previously reported, including the only treatment-related death at 53 days from a posttransplant lymphoproliferative disorder (patient 9).[9,18] Three other patients died of pneumonia in the setting of advanced disability and further loss of neurological function, one of whom had died at day +724 and had been previously reported (patient 16).[9] A second patient died at day +940 (patient 14). Both these patient met EDSS-failure endpoints for loss of neurological function before their deaths. The third patient who had previously been lost to follow-up at +3 months (patient 8) and who had a baseline EDSS of 8.0, died at +2645 days, beyond the time at which the neurological assessments were completed and beyond the time at which any other patient had follow-up information. The estimated 5-year overall survival was 86%. At 7 years, one patient was diagnosed with myelodysplastic syndrome. He had failed a course of mitoxantrone therapy before proceeding to HDIT. If EDSS failures and deaths without EDSS failure are combined, then the estimate of EDSS-failure-free survival at 72 months was 44% (95% CI, 22–66%).

Discussion

We had previously identified important clinical issues specific to MS patients treated with HDIT and AHCT.[9,18] Changes were made to improve the safety of the HDIT procedure including the administration of corticosteroids during mobilization and after transplant to reduce the risk of a G-CSF-mediated MS flare and engraftment syndrome.[19] In our previous

report, the estimate of EDSS failure at +3 years was 27%. With additional follow-up data, the estimate of EDSS failure at 3 years was now 40% and at 6 years was 52%. Even though some patients continued to fail treatment with longer follow-up, there was a marked decline in MRI activity. This observation is similar to those of other studies in which a subset of patients with advanced MS continued to have a steady decline in neurological function after HDIT and AHCT even though there was little clinical evidence of ongoing inflammation. There are few published data on patient outcomes after HDIT and AHCT with a median follow-up of 4 years. Fassas et al. reported that with a median follow-up of 35 months, progression-free survival was 81% at 60 months.[20] In a recent long-term follow-up report from this same group, disease progression-free survival at 15 years was 44% with active CNS disease pretransplant and 10% for those without[21]. The difference in outcomes based on disease activity at baseline could not be confirmed in the current study. At a median follow-up of 36 months, the Italian GITMO-Neuro Intergroup noted a 95% progression-free survival at 4.5 years and 64% of patients were free from disease activity.[22] Researchers from Beijing and Russia reported estimated progression-free survivals of 64% at 49 months (median follow-up: 35 months) and 72% at 72 months after HDIT (mean follow-up: 19 months), respectively.[23,24] Krasulova et al. reported that 71% and 29% of patients were free from progression at 3 and 6 years of follow-up, respectively[25]. These overall findings are mirrored in a report from a European registry.[26] Our report contributes to the long-term experience and shows that a significant number of patients remained stable at six years but that worsening of neurological function continued to occur as late as 5 years after study treatment.

It is uncertain why treatment failed in 11 of 26 patients, but it may reflect the advanced disease status of many of these patients at baseline. It has been noted that patients with EDSS scores 6.0 fared better than those with higher levels of disability and that progression-free survival was much better in patients <40 years of age and who were treated within 5 years of diagnosis.[26,27] This view is supported by our data, where patients who worsened did so in the absence of clinical attacks or MRI activity and only one of five patients with a baseline EDSS 6.0 failed treatment. Non-inflammatory mechanisms of the disease may continue to be active even after aggressive immunosuppressive treatment. HDIT and AHCT may be more effective for patients with aggressive forms of RRMS.[28–30] In a larger series of patients with aggressive RRMS, it was shown that all of the patients were free from progression, and 62% of patients were free from disease activity at +3 years.[31] These observations, although still limited, would suggest that HDIT and AHCT can be effective for controlling the inflammatory elements of the 'early' MS disease process.

OCB are two or more bands of IgG in the CSF and are present in 85–90% of MS patients. They are produced from clonally expanded B cells in the CNS and persist indefinitely as a non-specific marker of the disease.[32] We had previously reported that three patients who were positive for OCB at baseline became negative after HDIT and AHCT using agarose electrophoresis.[9] Using the more sensitive approach of IEF, we determined that 2 of these 3 patients remained positive for OCB. CSF from the third patient was not available for repeat OCB testing. With some exceptions, OCB have been observed to persist in other studies of HDIT and AHCT for MS.[22,30,33–36] However, it has been reported that in the brains of patients who died after HDIT and AHCT, there were very few T cells and a complete

absence of B cells and plasma cells in MS lesions.[37] In all reported cases of OCB after AHCT except one, the repeat LP was done within 12 months of the AHCT. Since antibody in the CSF may be long-lived even if B cells in the CNS are depleted, we tested the CSF of two patients at 4 and 6 years after study treatment to assess if the OCB persisted. CSF from three other patients had been studied at 2 years after study treatment. Persistent OCB were observed late after AHCT in all 5 patients even though patients may have improved neurologically. Although the presence of OCB at 2 years and beyond indicates that the clonally expanded B cells have persisted despite HDIT, OCB have not been shown to be useful biomarkers of disease response after conventional MS treatments and have not been used for this purpose. It is therefore uncertain if the persisting OCB have any clinical significance with regards to the durability of response to treatment.

There were two other studies that used TBI as part of a high-dose immunosuppressive regimen for MS. Burt et al reported that 8 of 12 patients with a baseline EDSS of >6.0 and 0 of 9 patients with a baseline EDSS of 6.0 had failed treatment with a TBI dose of 1200 cGy.[27] Samijn et al. found that only 36% of patients were neurologically stable at 36 months with a regimen that used 1000 cGy.[38] The investigators in these two studies raised a concern about the potential neurotoxic effects of TBI. We did not observe any neurotoxic effects at the lower dose of 800 cGy TBI that could be differentiated from the primary disease process or other events which occurred after transplant. In a recent meta-analysis, high-intensity regimens including those with TBI were not as effective as intermediate-intensity immunosuppressive regimens.[39] Since TBI does not seem to contribute to better outcomes than that reported for non-TBI-based regimens and considering the concern about neurotoxicity and secondary malignancies, high-dose immunosuppression with intermediate-intensity chemotherapy-only regimens is preferable for future studies.

A decrease in brain volume has been described previously with high-dose cytotoxic therapies for patients with hematological malignancies.[40] In MS patients, the decrease in brain volume is most prominent during the first month after HDIT and then later in the first 2 years after HDIT is comparable to the baseline rates.[41] Rates of brain volume loss may further decrease towards normal beyond 2 years.[42] We have confirmed that brain volume decreases after HDIT but could not confirm with the limited data available that brain volume loss stabilizes beyond 2 years from treatment.

Similar to other published reports, the limitations of our pilot study include the absence of a control group. A comparison with historical controls was not possible since there is limited historical data on clinical outcomes for patients with aggressive, advanced MS. Another limitation was that a small number of patients were lost for the follow-up phase of the study. Furthermore, study visits after 2 years were less frequent and more irregular than in the first 2 years so that use of confirmed disability as the EDSS-failure endpoint was thus more problematic. Requiring a non-confirmed increase in EDSS of 1.0 point instead of 0.5 points reduced the likelihood that the primary endpoint of EDSS failure was resulting from other factors besides a decline in neurological function especially at the last study visit.

Treatment of aggressive advanced MS with HDIT and AHCT may lead to stabilization of the disease in some patients for as long as six years. The procedure was not associated with

significant late complications, although one patient previously treated with mitoxantrone developed myelodysplastic syndrome. The continued worsening of neurological function in 11 of the 26 patients, with limited evidence of new lesions on MRI or clinical exacerbations, indicates that non-inflammatory factors may continue to be active. This suggests that the treatment may be more successful if instituted in earlier stages of the disease. In order to address this question, it is important to study HDIT followed by AHCT in MS subjects who are still in the active inflammatory stage of their relapsing/remitting course.

Acknowledgments

References

1. Frischer JM, Bramow S, Dal Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009; 132:1175–1189. [PubMed: 19339255]

2. Reingold SC, Steiner JP, Polman CH, Cohen JA, Freedman MS, Kappos L, et al. The challenge of follow-on biologics for treatment of multiple sclerosis (Review). Neurology. 2009; 73:552–559. [PubMed: 19687456]

3. Karussis D, Vourka-Karussis U, Mizrachi-Koll R, Abramsky O. Acute/relapsing experimental autoimmune encephalomyelitis: induction of long lasting, antigen-specific tolerance by syngeneic bone marrow transplantation. Multiple Sclerosis. 1999; 5:17–21. [PubMed: 10096098]

4. Nash RA, McSweeney PA, Crofford LJ, Abidi M, Chen C-S, Godwin JD, et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the U.S. multicenter pilot study. Blood. 2007; 110:1388–1396. [PubMed: 17452515]

5. Vonk MC, Marjanovic Z, van den Hoogen FH, Zohar S, Schattenberg AV, Fibbe WE, et al. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. Ann Rheum Dis. 2008; 67:98–104. [Erratum appears in Ann Rheum Dis. 2008 Feb;67(2): 280]. [PubMed: 17526554]

6. Burt RK, Traynor A, Statkute L, Barr WG, Rosa R, Schroeder J, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA. 2006; 295:527–535. [PubMed: 16449618]

7. Brinkman DM, de Kleer IM, Ten Cate R, Van Rossum MA, Bekkering WP, Fasth A, et al. Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial. Arthritis Rheum. 2007; 56:2410–2421. [PubMed: 17599770]

8. van Bekkum DW. Conditioning regimens for the treatment of experimental arthritis with autologous bone marrow transplantation. Bone Marrow Transplant. 2000; 25:357–364. [PubMed: 10723577]

9. Nash RA, Bowen JD, McSweeney PA, Pavletic SZ, Maravilla KR, Park M-S, et al. High-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation for severe multiple sclerosis. Blood. 2003; 102:2364–2372. [PubMed: 12763935]

10. Storek J, Zhao Z, Lin E, Berger T, McSweeney PA, Nash RA, et al. Recovery from and consequences of severe iatrogenic lymphopenia (induced to treat autoimmune diseases). Clinical Immunology. 2004; 113:285–298. [PubMed: 15507394]

11. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol. 1983; 13:227–231. [PubMed: 6847134]

12. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology. 1996; 46:907–911. [PubMed: 8780061]

13. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983; 33:1444–1452. [PubMed: 6685237]

14. Rowley SD, Loken M, Radich J, Kunkle LA, Mills BJ, Gooley T, et al. Isolation of CD34+ cells from blood stem cell components using the Baxter isolex system. Bone Marrow Transplant. 1998; 21:1253–1262. [PubMed: 9674860]

15. Freedman MS, Thompson EJ, Deisenhammer F, Giovannoni G, Grimsley G, Keir G, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. Arch Neurol. 2005; 62:865–870. [PubMed: 15956157]

16. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18:695–706. [PubMed: 10204198]

17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457–481.

18. Nash RA, Dansey R, Storek J, Georges GE, Bowen JD, Holmberg LA, et al. Epstein-barr virus-associated posttransplantation lymphoproliferative disorder after high-dose immunosuppressive therapy and autologous CD34-selected hematopoietic stem cell transplantation for severe autoimmune diseases. Biol Blood Marrow Transplant. 2003; 9:583–591. [PubMed: 14506660]

19. Openshaw H, Stuve O, Antel JP, Nash R, Lund BT, Weiner LP, et al. Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. Neurology. 2000; 54:2147–2150. [PubMed: 10851379]

20. Fassas A, Kimiskidis VK. Stem cell transplantation for multiple sclerosis: what is the evidence? (Review). Blood Rev. 2003; 17:233–240. [PubMed: 14556778]

21. Fassas A, Kimiskidis VK, Sakellari I, Kapinas K, Anagnostopoulos A, Tsimourtou V, et al. Long-term results of stem cell transplantation for MS: a single-center experience. Neurology. 2011; 76:1066–1070. [PubMed: 21422458]

22. Saccardi R, Mancardi GL, Solari A, Bosi A, Bruzzi P, Di Bartolomeo P, et al. Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life. Blood. 2005; 105:2601–2607. [PubMed: 15546956]

23. Su L, Xu J, Ji BX, Wan SG, Lu CY, Dong HQ, et al. Autologous peripheral blood stem cell transplantation for severe multiple sclerosis. Int J Hematol. 2006; 84:276–281. [PubMed: 17050205]

24. Shevchenko YL, Novik AA, Kuznetsov AN, Afanasiev BV, Lisukov IA, Kozlov VA, et al. High-dose immunosuppressive therapy with autologous hematopoietic stem cell transplantation as a treatment option in multiple sclerosis. Exp Hematol. 2008; 36:922–928. [PubMed: 18468768]

25. Krasulova E, Trneny M, Kozak T, Vackova B, Pohlreich D, Kemlink D, et al. High-dose immunoablation with autologous haematopoietic stem cell transplantation in aggressive multiple sclerosis: a single centre 10-year experience. Multiple Sclerosis. 2010; 16:685–693. [PubMed: 20350962]

26. Saccardi R, Kozak T, Bocelli-Tyndall C, Fassas A, Kazis A, Havrdova E, et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. Multiple Sclerosis. 2006; 12:814–823. [PubMed: 17263012]

27. Burt RK, Cohen BA, Russell E, Spero K, Joshi A, Oyama Y, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. Blood. 2003; 102:2373–2378. [PubMed: 12842989]

28. Mancardi GL, Murialdo A, Rossi P, Gualandi F, Martino G, Marmont A, et al. Autologous stem cell transplantation as rescue therapy in malignant forms of multiple sclerosis. Multiple Sclerosis. 2005; 11:367–371. [PubMed: 15957523]

29. Fagius J, Lundgren J, Oberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation. Multiple Sclerosis. 2009; 15:229–237. [PubMed: 18805841]

30. Kimiskidis V, Sakellari I, Tsimourtou V, Kapina V, Papagiannopoulos S, Kazis D, et al. Autologous stem-cell transplantation in malignant multiple sclerosis: a case with a favorable long-term outcome. Multiple Sclerosis. 2008; 14:278–283. [PubMed: 17942513]

31. Burt RK, Loh Y, Cohen B, Stefoski D, Balabanov R, Katsamakis G, et al. Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. Lancet Neurology. 2009; 8:244–253. [Erratum appears in Lancet Neurol. 2009 Apr;8(4):309]. [PubMed: 19186105]

32. Obermeier B, Mentele R, Malotka J, Kellermann J, Kumpfel T, Wekerle H, et al. Matching of oligoclonal immunoglobulin transcriptomes and proteomes of cerebrospinal fluid in multiple sclerosis. Nat Med. 2008; 14:688–693. [PubMed: 18488038]

33. Openshaw H, Lund BT, Kashyap A, Atkinson R, Sniecinski I, Weiner LP, et al. Peripheral blood stem cell transplantation in multiple sclerosis with busulfan and cyclophosphamide conditioning: report of toxicity and immunological monitoring. Biol Blood Marrow Transplant. 2000; 6:563–575. [PubMed: 11071262]

34. Carreras E, Saiz A, Marin P, Martinez C, Rovira M, Villamor N, et al. CD34+ selected autologous peripheral blood stem cell transplantation for multiple sclerosis: report of toxicity and treatment results at one year of follow-up in 15 patients. Haematologica. 2003; 88:306–314. [PubMed: 12651270]

35. Mondria T, Lamers CH, te Boekhorst PA, Gratama JW, Hintzen RQ. Bone-marrow transplantation fails to halt intrathecal lymphocyte activation in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2008; 79:1013–1015. [PubMed: 18223013]

36. Portaccio E, Amato MP, Siracusa G, Pagliai F, Sorbi S, Guidi S, et al. Autologous hematopoietic stem cell transplantation for very active relapsing-remitting multiple sclerosis: report of two cases. Multiple Sclerosis. 2007; 13:676–678. [PubMed: 17548451]

37. Metz I, Lucchinetti CF, Openshaw H, Garcia-Merino A, Lassmann H, Freedman MS, et al. Autologous haematopoietic stem cell transplantation fails to stop demyelination and neurodegeneration in multiple sclerosis. Brain. 2007; 130:1254–1262. [PubMed: 17293360]

38. Samijn JP, te Boekhorst PA, Mondria T, van Doorn PA, Flach HZ, van der Meche FG, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. J Neurol Neurosurg Psychiatry. 2006; 77:46–50. [PubMed: 16361591]

39. Reston JT, Uhl S, Treadwell JR, Nash RA, Schoelles K. Autologous hematopoietic cell transplantation for multiple sclerosis: a systematic review. Multiple Sclerosis. 2011; 17:204–213. [PubMed: 20921236]

40. Jager HR, Williams EJ, Savage DG, Rule SA, Hajnal JV, Sikora K, et al. Assessment of brain changes with registered MR before and after bone marrow transplantation for chronic myeloid leukemia. Am J Neurorad. 1996; 17:1275–1282.

41. Chen JT, Collins DL, Atkins HL, Freedman MS, Galal A, Arnold DL, et al. Brain atrophy after immunoablation and stem cell transplantation in multiple sclerosis. Neurology. 2006; 66:1935–1937. [PubMed: 16801665]

42. Roccatagliata L, Rocca M, Valsasina P, Bonzano L, Sormani M, Saccardi R, et al. The long-term effect of AHSCT on MRI measures of MS evolution: a five-year follow-up study. Multiple Sclerosis. 2007; 13:1068–1070. [PubMed: 17468445]
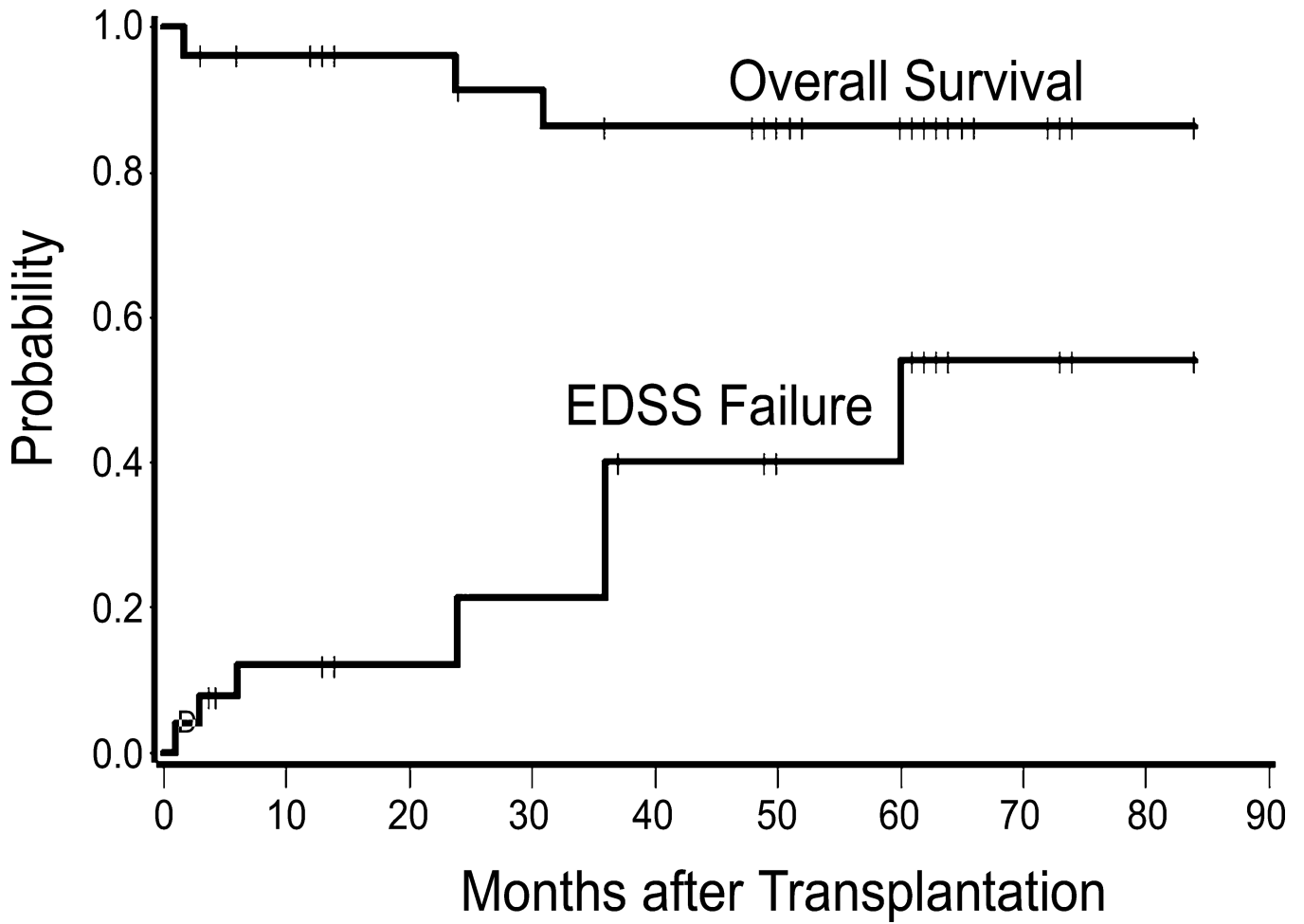
Figure 1.
Overall survival and EDSS failure after high-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for MS. EDSS failure was defined as an increase in the EDSS by   1 point on any two consecutive measures or at last assessment with the time of failure being the first of such assessments. Tick marks represent censored observations, and the "D" in the EDSS-failure curve represents a death without EDSS failure.
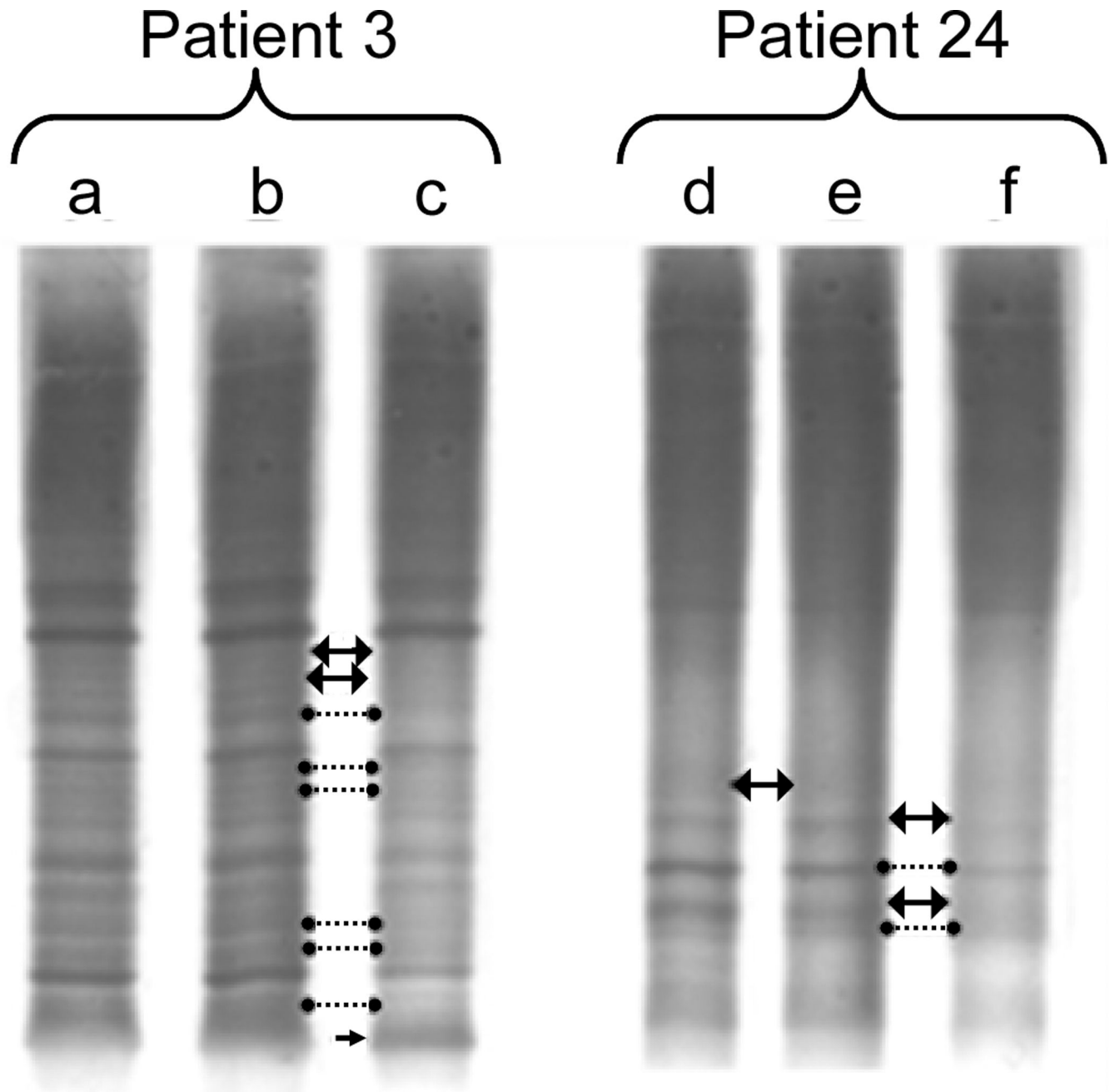
Figure 2.
Oligoclonal bands in cerebrospinal fluid before and after high-dose immunosuppressive
therapy and autologous hematopoietic cell transplantation. Oligoclonal banding pattern of
cerebrospinal fluid (CSF) after long-term follow-up of +6 and +4 years for patient 3 and
patient 24, respectively. CSF samples from patient 3: baseline (**a**), +1 year (**b**) and +6 years
(**c**). CSF samples from patient 24: baseline (**d**, +1 year (**e**) and +4 years (**f**). Some CSF bands
were less prominent and less distinct (dotted lines) or no longer visible (double arrowheads)
in later samples, but the overall impression was that the oligoclonal banding pattern
remained relatively stable, suggesting little effect of HDIT on clonally expanded B or

plasma cells in the central nervous system. A single band (single arrowhead) appeared to be more prominent in the sample obtained at +6 years from patient 3 than in earlier samples. Paired sera drawn at the time of the lumbar puncture were available for 5 of the 6 CSF samples. Although a minor degree of oligoclonal banding was present in some of the sera, the serum bands did not account for the bands in the CSF.

Table 1

EDSS results at baseline and over time following HDIT

Patient no.	MS type	Gender	Age	Months after HDIT											Comments
				0	1	3	6	12	24	36	48	60	72	84	
1	SP	F	34	8	8	8	8	8	8.5	8				8.5	
2	SP	F	49	6.5	6.5	6	4	3.5	6			6	6		
3	PP	M	37	6	6	6	5.5	5.5	6	6		3.5			
4	RR	F	46	7	7.5	8	6.5	6.5	6	6.5	6.5	6.5	7		
5	SP	M	35	6	6	6	6	6	6		6.5				
6	SP	F	37	6	6.5	7.5	6.5	7.5				6.5			
7	SP	F	51	7	7	7.5	**8**	**8**	**9**	**9**					
8	SP	F	48	8	7.5	8									Lost to follow-up. Died +2645 days
9	SP	F	57	7											Died +53 days
10	PP	M	51	6.5	6.5	6.5	6.5	6.5	6.5	**7.5**	**8**	**8**			
11	SP	F	47	8	8	8	8	8.5	8	**9**		**9**			
12	SP	M	38	6.5	6.5	6.5	6.5	6.5	**7.5**						Lost to follow-up.
13	SP	F	29	6.5	6	6.5	6.5	6.5	7	**7.5**	**7.5**				
14	PP	M	43	7	7	6.5	7	7.5	**8**						Died +940 days
15	PP	M	27	7.5	8	7.5	8	8	7.5		7	7			
16	SP	M	60	7.5	**8.5**	**8.5**	**8.5**	**8.5**							Died +724 days
17	SP	F	44	7.5	8	7.5	7.5	7.5	8			**8.5**			
18	SP	F	47	7.5	7.5	7	7	7.5	7.5		8	8			
19	SP	M	29	5	6.5	5	4.5	4.5	5.5			**6.5**			
20	PP	M	36	6.5	6	6	6	6	6.5	6.5					
21	SP	M	45	8	7.5	7	7.5	8	8	8	8				
22	PP	M	44	6.5	6.5	6.5	6	6							Lost to follow-up.
23	PP	M	52	5	5	5	5.5	5							Lost to follow-up.
24	PP	M	28	7	7	**8**	**8**	**8**		**8**	**7.5**				
25	SP	F	47	8	8	8									Lost to follow-up.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Patient no.	MS type	Gender	Age	Months after HDIT												Comments
				0	1	3	6	12	24	36	48	60	72	84	
26	SP	M	41	7	7	7	7	7		8.5	8.5				

The highlighted cells indicate the study visits when the EDSS was ≥ 1 above baseline and patient met the endpoint of treatment failure.