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TRIAL OF HIGH DOSE IMMUNOSUPPRESSIVE THERAPY WITH HEMATOPOIETIC STEM CELL SUPPORT IN DEVIC'S DISEASE

Principal Investigator:

Richard K. Burt, M.D., Chief
Division of Immunotherapy, Northwestern University, Chicago, USA

Co-Investigators:

Roumen Balabanov, M.D.
Rush University Multiple Sclerosis Center, Chicago, USA

Kimberly Yaung Grady, R.N.
Division of Immunotherapy, Northwestern University, Chicago, USA

Kate Quigley, R.N., M.B.A.
Division of Immunotherapy, Northwestern University, Chicago, USA

Robert Sufit, M.D.
Department of Neurology, Northwestern University, Chicago, USA

Statistician:

Borko Jovanovic, Ph.D., Northwestern University, Chicago, USA

TABLE OF CONTENTS

1.0 Precis

Neuromyelitis optica (NMO, Devic's disease) is an autoimmune, inflammatory, demyelinating central nervous system disorder in which a person's own immune system attacks the optic nerves and spinal cord and is characterized by concurrence of optic neuritis and transverse myelitis, typically associated with a lesion in the spinal cord extending over three or more vertebral segments. Although it is most commonly relapsing, it is distinct from multiple sclerosis in that it is more severe, tends to spare the brain, and is associated with a longitudinally extensive lesion on spinal cord MRI. Furthermore, NMO is associated with a highly specific serum autoantibody marker, NMO-IgG, which targets the water channel aquaporin-4. The disease follows a relapsing course in more than 90% of patients. Vision and ambulation are significantly impaired within 5 years of its onset in approximately half of patients (46). Relapses usually occur early with about 55% of patients having a relapse in the first year and 90% in the first 5 years (47). Unlike MS, Devic's disease rarely has a secondary progressive phase in which patients have increasing neurologic decline between attacks without remission. Instead, disabilities arise from the acute attacks (47).
Approximately 20% of patients with monophasic Devic's disease have permanent visual loss and 30% have permanent paralysis in one or more legs. Among patients with relapsing Devic's disease, 50% have paralysis or blindness within 5 years. In some patients (33% in one study), transverse myelitis in the cervical spinal cord resulted in respiratory failure and subsequent death (47).
At present, parenteral corticosteroids are widely employed as first-line treatment of optic neuritis and myelitis attacks, whereas therapeutic plasmapheresis is applied in the case of corticosteroids failure. Various strategies for the prevention of NMO relapses have been employed in small case series with modest activity. Immune based therapies, in order to be effective, need to be started early in the disease course while Devic's disease is predominantly an immune-mediated and inflammatory disease. Since 50% of patients with NMO are confined to a wheelchair within 5 years of onset, new therapies are needed in this disease.
We now propose, as a phase I study, complete immune ablation and subsequent reconstitution with autologous stem cells.

2.0 Objectives

To evaluate the safety (phase I) of autologous hematopoietic stem cell transplantation for inflammatory, autoimmune and demyelinating NMO. The primary endpoints to be considered in this study are:

2.1 Primary Endpoint:

1. Survival.
2. ~~Visual acuity.~~
3. ~~Decreased weakness in limb (MRC) (see appendix).~~

2.2 Secondary Endpoints:

1. Number of acute attacks.
2. Time to confinement in a wheelchair.
3. Time to legal blindness (visual acuity of 20/200 or less in the better eye with the best correction possible).
4. Disability scores (disease improvement defined by at least a 1 point increase in the EDSS on consecutive evaluations at least 3 months apart).

5. Quality of life- SF –36.
6. NMO – IgG aquaporin – 4 autoantibody titer.

3.0 Background of Devic's disease

Devic's disease is similar to MS in that the body's immune system attacks the myelin surrounding nerve cells. Unlike standard MS, the attacks are not believed to be mediated by the immune system's T cells but rather by antibodies called NMO-IgG. These antibodies target a protein called aquaporin 4 in the cell membranes of astrocytes which acts as a channel for the transport of water across the cell membrane. (28) Aquaporin 4 is found in the processes of the astrocytes that surround the blood-brain barrier, a system responsible for preventing substances in the blood from crossing into the brain. The blood-brain barrier is weakened in Devic's disease, but it is currently unknown how the NMO-IgG immune response leads to demyelination.

Most research into the pathology of Devic's disease has focused on the spinal cord. The damage in the spinal cord can range from inflammatory demyelination to necrotic damage of the white and grey matter. The inflammatory lesions in Devic's disease have been classified as type II lesions (complement mediated demyelinization), but they differ from MS pattern II lesions in their prominent perivascular distribution. Therefore, the pattern of inflammation is often quite distinct from that seen in MS. (28) (33)

3.1 Diagnosis

The Mayo Clinic proposed a revised set of criteria for diagnosis of Devic's disease in 2006. The new guidelines for diagnosis require two absolute criteria plus at least two of three supportive criteria being: (34)

Absolute criteria:

1. Optic neuritis
2. Acute myelitis

Supportive criteria:

1. Brain MRI not meeting criteria for MS at disease onset
2. Spinal cord MRI with contiguous T2-weighted signal abnormality extending over 3 or more vertebral segments, indicating a relatively large lesion in the spinal cord
3. NMO-IgG seropositive status. The NMO-IgG test checks the existence of antibodies against the aquaporin 4 antigen.

3.1.2 Variants

After the development of the NMO-IgG test, the spectrum of disorders that comprise Devic's disease was expanded. The Devic's disease spectrum is now believed to consist of:

- Standard Devic's disease, according to the diagnostic criteria described above
- Limited forms of Devic's disease, such as single or recurrent events of longitudinally extensive myelitis, and bilateral simultaneous or recurrent optic neuritis
- Asian optic-spinal MS
- Longitudinally extensive myelitis or optic neuritis associated with systemic auto-immune disease
- Optic neuritis or myelitis associated with lesions in specific brain areas

such as the hypothalamus, periventricular nucleus, and brainstem (35)

Whether Devic's disease is a distinct disease or part of the wide spectrum of multiple sclerosis is debated. Devic's disease differs in that it usually has more severe sequelae after an acute episode than in MS, MS infrequently presents as transverse myelitis, while oligoclonal bands in the CSF, as well as white matter lesions on brain MRI, are uncommon in Devic's disease but occur in over 90% of MS patients. (36)

3.1.3 Proposed diagnostic criteria for neuromyelitis optica* (76)

Absolute criteria:
1. Optic neuritis
2. Acute myelitis
3. No evidence of clinical disease outside of the optic nerve or spinal cord

Supportive criteria:
Major
1. Negative brain MRI at onset
2. Spinal cord MRI with signal abnormality extending over 3 vertebral segments
3. CSF pleocytosis of >50 WBC/mm or > 5 neutrophils/mm

Minor
1. Bilateral optic neuritis
2. Severe optic neuritis with fixed visual acuity worse than 20/200 in at least one eye
3. Severe, fixed, attack-related weakness (MRC <2) in one or more limbs

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*Diagnosis requires all absolute criteria and one major supportive criterion or two minor supportive criteria.
WBC = white blood cell count; MRC = Medical Research Council

3.2 Treatment of attacks

Attacks are treated with short courses of high dosage intravenous corticosteroids such as methylprednisolone IV. When attacks progress or do not respond to corticosteroid treatment, plasmapheresis can be an effective treatment. (35) Clinical trials for these treatments contain very small numbers, and most are uncontrolled.

3.3 Secondary prevention

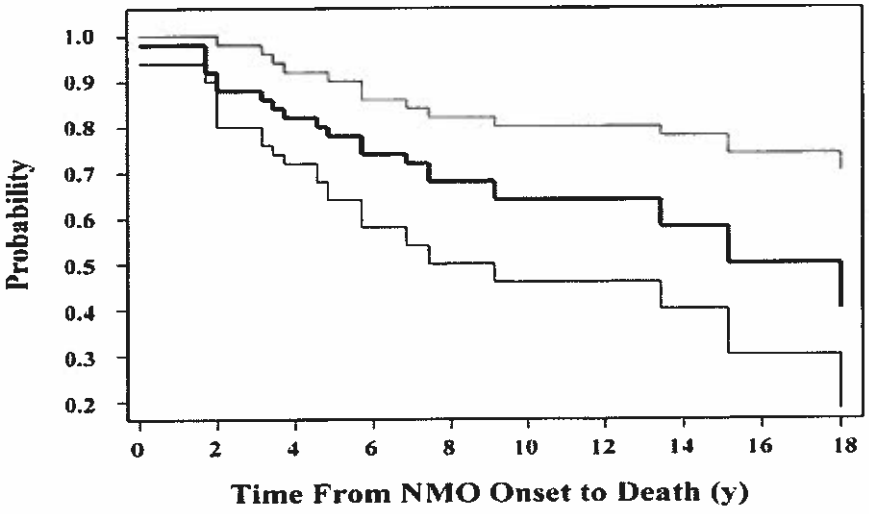
No controlled trials have established the effectiveness of treatments for the prevention of attacks. Many clinicians agree that long term immunosuppression is required to reduce the frequency and severity of attacks, while others argue the exact opposite (38). Commonly used immunosuppressant treatments include azathioprine (Imuran) plus prednisone, mycophenolate mofetil plus prednisone, Rituximab, Mitoxantrone, intravenous immunoglobulin (IVIG), and Cyclophosphamide (39) (35). The monoclonal antibody rituximab is under study (40). In 2007, Devic's disease was reported to be responsive to glatiramer acetate (41) and to low-dose corticosteroids. (42)

3.4 Prognosis

Normally, there is some measure of improvement in a few weeks, but residual signs and disability may persist, sometimes severely.
The disease can be monophasic, i.e. a single episode with permanent remission. However, at least 85% of patients have a relapsing form of the disease with repeated attacks of transverse myelitis and/or optic neuritis. In patients with the monophasic form the transverse myelitis and optic neuritis occur simultaneously or within days of each other. On the other hand, patients with the relapsing form are more likely to have weeks or months between the initial attacks and to have better motor recovery after the initial transverse myelitis event. Relapses usually occur early with about 55% of patients having a relapse in the first year and 90% in the first 5 years. (28) Unlike MS, Devic's disease rarely has a secondary progressive phase in which patients have increasing neurologic decline between attacks without remission. Instead, disabilities arise from the acute attacks. (28)
Approximately 20% of patients with monophasic Devic's disease have permanent visual loss and 30% have permanent paralysis in one or more legs. Among patients with relapsing Devic's disease, 50% have paralysis or blindness within 5 years. In some patients (33% in one study), transverse myelitis in the cervical spinal cord resulted in respiratory failure and subsequent death.
It is clinically important to identify risk factors that predict a relapsing course as early as possible, ideally after the NMO diagnostic criteria are met, in order that immunomodulatory therapy can be started prior to accumulation of severe neurologic deficit. It is established that female sex, older age at onset, presence of systemic autoimmunity were each independently associated with a relapsing course. Prediction of disease course is highly desirable because those with monophasic disease will not require therapeutic interventions aimed at relapse prevention. (78)

3.5 Figure 1

Relapsing Devic's- Probability of survival



Relapsing neuromyelitis optica (NMO) survival: time from disease onset to death. Nonparametric survival curve for relapsing NMO survival. Median survival = 17.4 years. Bold line is probability estimate; lighter lines are 95 % CI's. (76)

3.6 Epidemiology

The prevalence and incidence of Devic's disease has not been established partly because the disease is under recognized and often confused with MS (28). Devic's disease is more common in women than men, with women comprising over 2/3 of patients and more than 80% of those with the relapsing form of the disease. (28)
Devic's disease is more common in Asiatic people than Caucasians. In fact, Asian optic-spinal MS (which constitutes 30% of the cases of MS in Japan) has been suggested to be identical to Devic's disease (Differences between optic-spinal and classic MS in Japanese patients). In the indigenous populations of tropical and subtropical regions, MS is rare, but when it appears it often takes the form of optic-spinal MS (43).
The majority of Devic's disease patients have no affected relatives, and it is generally regarded as a non-familial condition. (28)

4.0 Rationale for the Proposed Treatment and Scientific Justification

The rationale for autologous HSCT of autoimmune diseases is to regenerate a new, i.e. antigen naïve immune system, from the patient's own hematopoietic stem cell. Intense immune ablation without myeloablative side effects could be accomplished with agents such as cyclophosphamide, fludarabine, and antibodies to T cells (anti-thymocyte globulin) and / or B cells (rituximab) or both T and B cells (Campath). Non-myeloablative autologous HSCT regimens are safer and pose less risk to the patient than myeloablative regimens.
The initial standard non-myeloablative regimen consisted of cyclophosphamide and rabbit antithymocyte globulin (r ATG) and was pretty well tolerated. A second generation non-myeloablative regimen included cyclophosphamide and a broader and longer acting agent, Alemtuzumab, instead of r ATG. After transplantation in patients, receiving regimens, containing Alemtuzumab, potential life-threatening secondary autoimmune cytopenias, including idiopathic thrombocytopenic purpura, autoimmune neutropenia, and autoimmune hemolytic anemia, occurred late (2 to 18 months). (76)
And to date, the third generation non-myeloablative regimen, termed "Rituximab sandwich", has been well tolerated. This regimen entails 1 dose of Rituximab given before and after cyclophosphamide and r ATG.
(77)
Autologous HSCT for autoimmune diseases may be performed with either myeloablative or nonmyeloablative regimens. (74). Myeloablative regimens use cancer-specific treatments that destroy the entire marrow compartment, including marrow stem cells, resulting in irreversible and lethal marrow failure if HSCs are not reinfused. Nonmyeloablative regimens are designed specifically for autoimmune diseases, i.e., for lymphoablation without irreversible destruction of marrow stem cells. Following a nonmyeloablative regimen, hematopoietic recovery will occur without infusion of HSCs; however, autologous HSCs provide support and shorten the duration of chemotherapy-induced marrow suppression. (75).
Non-myeloablative regimen has a mortality of < 1% (table 1)

Table 1. Treatment –Related Mortality Following Autologous Hematopoietic Stem Cell Transplantation for Autoimmune Diseases (77), non-myeloablative regimen

Source	Disease	Multicenter Or Single Center	Treatment –Related Deaths/Patients No. (%)	Response
Burt et al	Relapsing-Remitting MS	Single	0/21 (0)	0%progression at 2years, 62% improved
Craig et al	Crohn's disease	Single	0/21 (0)	100% remission 33% relapse
Oyama et al	Systemic sclerosis	Single	0/10 (0)	70% progression-free Survival at 2 years
Statkute et al	Vasculitis	Single	0/4 (0)	Complete remission (n=3);partial response (n=1)
Voltarelli et al	Type 1 diabetes mellitus	Single	0/15 (0)	13/15 patients Insulin –free
Vonk et al	Systemic Sclerosis	Multiple	1/26 (4)	64% event-free Survival at 5 years
Burt et al	SLE	Single	1/50 (2)	50% disease-free Survival at 5 years
Snowden et al	Rheumatoid Arthritis	Multiple	0/73 (0)	50% ACR criteria 50 or Greater response in 12 m
Total			2/200 (<1)	

4.1 Selection of High Dose Immunosuppressive Therapy and Autologous HSCT Strategy for this trial

To justify any new therapy such as HSCT, the risk of dying from the disease must be higher than that expected from its treatment, or the morbidities associated with the disease must justify the treatment risks. Cyclophosphamide with or without ATG has been used to treat several patients with systemic lupus erythematosus and approximately 80 rheumatoid arthritis patients in Australia, Europe and America, again without mortality, and has been used for longer than a decade as the conditioning regimen of choice for the non-malignant disease, aplastic anemia.

At our center we have experience with a "third" generation non-myeloablative regimen termed "Rituximab sandwich" which entails 1 dose of Rituximab given before and after Cyclophosphamide and rATG, and has been used safely without unexpected toxicity.

Rituximab

It is chimeric murine/human monoclonal antibody to the CD20 molecule on B-lymphocytes. The molecule is combined with Fc fragment of human IgG I kappa immunoglobulin containing murine light- and heavy-chain variable region sequence and human constant region sequences. Adverse reactions caused by Rituximab include infusion reactions, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhytmias and renal failure. The infusion reactions can be treated with slowing or interruption of the infusion and supportive care (diphenhydramine, acetaminophen, IV saline or vasopressors). Other reactions include: nausea, vomiting, diarrhea, headache, myalgias, arthralgias, cough, rhinitis, bronchospasm, dyspnea, sinusitis, lymphopenia, neutropenia, thrombocytopenia, anemia, abdominal pain, back pain, throat irritation, asthenia, infection. Reactivation of hepatitis B virus and progression to fulminant hepatitis has been reported in patients with negative hepatitis B surface antigen, but positive hepatitis B surface antibody.

Cyclophosphamide

It is a common conditioning regimen with two decades of experience in the treatment of aplastic anemia, and has been used safely without reported mortality in the treatment of autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. Cyclophosphamide is a potent immunosuppressive agent that not only has less acute toxicity, it has less chronic side effects. Cyclophosphamide is not associated with late malignancies or cataracts

It is an alkylating agent that requires hepatic metabolism to the active metabolites, phosphoramide mustard and acrolein. These active metabolites react with nucleophilic groups. It is available as an oral or intravenous preparation. Bioavailability is 90% when given orally. The half-life of the parent compound is 5.3 hours in adults and the half-life of the major metabolite phosphoramide mustard is 8.5 hours. Liver or renal dysfunction will lead to prolonged serum half-life. CY is administered intravenously at a dosage of 60 mg/kg on each of two successive days (use adjusted ideal body weight if patient's actual body weight is greater than 100% ideal body weight). The major dose limiting side effect at high doses is cardiac necrosis. Hemorrhagic cystitis can occur and is mediated by the acrolein metabolite. This can be prevented by co-administration of MESNA or bladder

irrigation. Other notable side effects include nausea, vomiting, alopecia, myelosuppression and SIADH. Refer to institutional manuals for more information about administration, toxicity and complications.

Rabbit- Derived Anti-Thymocyte Globulin (r ATG)

Rabbit-derived anti-human thymocyte globulin (ATG) is a gamma globulin preparation obtained from hyperimmune serum of rabbits immunized with human thymocytes. ATG has been used predominately in solid organ transplant immunosuppressive regimens. ATG is a predominantly lymphocyte-specific immunosuppressive agent. It contains antibodies specific to the antigens commonly found on the surface of T cells. After binding to these surface molecules, ATG promotes the depletion of T cells from the circulation through mechanisms which include opsonization and complement-assisted, antibody-dependent, cell-mediated cytotoxicity. The plasma half-life ranges from 1.5-12 days. ATG is administered intravenously at a dose of 0.5 mg/kg recipient body weight on day -5 and at a dose of 1.0 mg/kg recipient body weight on days -4 and dose 1.5 mg/kg recipient body weight on days-3, -2, -1. Unlike equine ATG, rabbit ATG does not require a pre-infusion skin test to check for hypersensitivity. Methylprednisolone 250 mg will be given before every dose of ATG. Additional medications such as diphenhydramine may be given at the discretion of the attending physician. Although rare, the major toxicity is anaphylaxis; chills, fever, pruritus or serum sickness may occur.

Method of Harvesting Stem Cells

Based on the experience of the pilot studies, the current protocol will mobilize stem cells with granulocyte-colony stimulating factor (G-CSF) and cyclophosphamide and collect stem cells by apheresis. A subsequent bone marrow harvest will be performed only if needed to supplement the peripheral blood stem cells (PBSC). Based on experience of autoimmune flares in patients receiving G-CSF alone for mobilization, patients will be mobilized with cyclophosphamide 2.0 g/m^2 and G-CSF 5- 10 mcg /kg.

5.0 Eligibility

5.1 Inclusion Criteria

1. Age 16-65, at the time of pretransplant evaluation.
2. An established diagnosis of Devic's disease (more than one acute attack).
3. NMO- IgG aquaporin-4 autoantibody positive.

5.2 Exclusion Criteria

1. Paraplegia or quadriplegia and legal blindness (defined as visual acuity of 20/200 or less in the better eye with the best correction possible).
2. Any illness that in the opinion of the investigators would jeopardize the ability of the patient to tolerate aggressive chemotherapy.
3. Prior history of malignancy except localized basal cell, squamous skin cancer or carcinoma in situ of the cervix. Other malignancies for which the patient is judged to be cured, such as head and neck cancer, or breast cancer will be considered on an individual basis.
4. Positive pregnancy test.
5. Inability or unwillingness to pursue effective means of birth control. Effective birth control is defined as 1) refraining from all acts of vaginal intercourse (ABSTINENCE); 2) consistent use of birth control pills; 3) injectable birth control methods (Depo-Provera, Norplant); 4) tubal sterilization or male partner who has undergone vasectomy; 5) placement of an IUD (intrauterine device); or 6) use, with every act of intercourse, of diaphragm with contraceptive jelly and/or condoms with contraceptive foam.
6. Failure to willingly accept or comprehend irreversible sterility as a side effect of therapy.
7. $FEV_1/FVC < 60\%$ of predicted after bronchodilator therapy (if necessary).
8. DLCO < 50% of predicted.
9. Resting LVEF < 50 %.
10. Serum creatinine > 2.0 mg/dl.
11. Known hypersensitivity to mouse, rabbit, or E. coli derived proteins.
12. Presence of metallic objects implanted in the body that would preclude the ability of the patient to safely have MRI exams.
13. Bilirubin > 2.0 mg/dl.
14. Platelet count < 100,000/up or ANC< 1000/up
15. Psychiatric illness, mental deficiency or cognitive dysfunction making compliance with treatment or informed consent impossible.
16. Active infection except asymptomatic bacteriuria.
17. Inability to give informed consent.
18. HIV positive.
19. Transaminases > 3x of normal limits, liver cirrhosis.

5.3 Study Procedures

	Baselin	During Hospitaliz daily	First 100 days after discharge from hospital	6 months after treatment	Every 12 months after treatment for 5 yrs.
Complete history and Physical exam	X	X	Weekly*	X	X
Disability Evaluation 9 hole peg test, timed 25-foot walk, EDSS, NRS, PASAT,MRC	X		X	X	X
MRI – Head & Spine with gadolinium	X				X May do only orbit & spine
CBC and diff	X	X	Once every 1-2	X	X
PT and PTT	X				
Serum chemistry .	X	X	Once every 1-2	X	X
HIV1 and HIV2	X				
Serum or Urine Pregnancy Test	X				
PFT w/ DLCO & FEVI/FVC	X				
2 D echo	X				
Chest X ray	X				
EKG	X				
Urinalysis	X				
Quantiferon Gold	X				
TSH, T3, T4	X				
Serologies Hepatitis A,B,C, Herpes, CMV	X				

JC virus titer	X				
QOL Questionnaires SF-36 and the FACT BMT	X			X	X
Dental Consult	X				
Anti-NMO	X			X	X
Ophthalmology evaluation	X				X

*** Until clinically stable**

5.4 Outcome Measurement Tools - Neuropsychological, Quality of Life (QOL), and Other Tests

All subjects will be examined (baseline) and yearly thereafter with neuropsychological exams which shall include the Paced Auditory Serial Addition Test (PASAT) and a standardized, repeatable battery of tests consisting of the Selective Reminding Test (verbal learning), 7/24 Spatial Recall Test I (visuospatial learning), and Controlled Oral Word Association (verbal fluency and semantic retrieval). These cognitive functions, in addition to the PASAT, are most often disrupted in patients with MS. Administration of these tests and MS Functional Composite (which includes timed 25-foot walk, and 9-hole peg test in addition to the PASAT) will be performed by a trained professional and should take 40 – 50 minutes. Self-administered quality of life exams (FACT-BMT and SF-36) will also be obtained pre-transplant, 6 and 12 months post-transplant, and then yearly until 5 years post-transplant.

The SF-36 (Ware 1997 and McHorney 1994) is a generic indicator of health status derived from the 245-item Medical Outcomes Study questionnaire. The SF-36 includes multi-item scales to measure the following eight dimensions; physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and general mental health (MH). The scoring system for each dimension uses an approach which recodes the answers of each question into a 0-to-100 score, oriented so that a higher score indicates a better health state. For example, functioning scales are scored such that a high score indicates better functioning and the pain scale is scored such that a higher score indicates decreased pain. The SF-36 is a commonly used quality of life measure and facilitates comparisons across treatments and disease groups as well as against population norms.

The FACT-BMT is a valid and reliable measure of five dimensions of quality of life in a HSCT recipients (McQuellon et al BMT 1997). It consists of the 35 question Functional Assessment of Cancer Therapy (FACT) measure and a 12 question BMT subscale. It is commonly used in BMT quality of life research. Although some of the questions are specific to HSCT recipients, the vast majority of questions in the scale apply equally to patients receiving any type of therapy for their illness. Along with providing additional comparative data between treatment groups, the FACT-BMT results will allow us to study the QOL in MS patients undergoing a HSCT versus other a HSCT populations from the literature.

6.0 Treatment Plan

6.1 Mobilization and Peripheral Blood Stem Cell Harvest:

Day	0	1	2	3	4	5	ANC>100/ul (approximately day 10)
Cytoxan 2.0 gm/m²	X						
G-CSF 5-						X	

10mcg/kg/day							
Hydration	X						
Mesna	X						
Apheresis							X*

Cytoxan dose of 2gm/m will be infused over two hours.

G-CSF- guidelines, 5-10 mcg/kg/day will be started day +5 and continued until the absolute neutrophil counts reaches at least 1,000

Hydration- guidelines, normal saline at 150-200ml/hr should be given 2 hours before cyclophosphamide and continued until 24 hours after the cyclophosphamide dose. The rate of hydration will be aggressively adjusted. BID weights will be obtained. Amount of fluid can be modified based on patient's fluid status.

Mesna, given the dose of 2.0 gm/m, infusion to be given over 24 hours.

*Apheresis will begin when the ANC is greater than 1000/ul and continue until greater than 2.0 x 10^6 $CD34^+$ cells/kg patient weight have been cryopreserved. A maximum of four apheresis will be performed. The G-CSF will continue until apheresis is discontinued.

6.2 Interval between Mobilization and Conditioning

In order to avoid cumulative cardiac toxicity from cyclophosphamide and to allow culture of HSC product, three weeks must separate the administration of cyclophosphamide for mobilization and for conditioning.

6.3 Transplant Conditioning Regimen

Day	-7	-6	-5	-4	-3	-2	-1	0	+1	+6
Hydration		X	X	X	X	X	X			
Cyclophosphamide 50 mg/kg/day			X	X	X	X				
MESNA 50 mg/kg/day			X	X	X	X				
rATG mg/kg/day			0.5	1.0	1.5	1.5	1.5			
Stem cell reinfusion								X		
Rituxan 500 mg		X							X	
Solu-Medrol 250 mg IV			X	X	X	X	X			
Apheresis catheter insertion*	X									
Plasmapheresis	X									

Temporary apheresis catheter placed by interventional radiology, will be removed after plasmapheresis

Hydration-guidelines: NS at 150-200 ml/hr should be given 2 hours before cyclophosphamide and continued until 24 hours after the last cyclophosphamide dose.

The rate of hydration will be aggressively adjusted. BID weights will be obtained. Amount of fluid can be modified based on patient's fluid status.

Cyclophosphamide: 50 mg/kg/day will be given IV over 2 hours in 500 cc of normal saline. If actual weight is < ideal weight, cyclophosphamide will be given based on actual weight. If actual weight is > ideal weight, cyclophosphamide will be given as adjusted weight. Adjusted weight = ideal weight + 25% (actual weight minus ideal weight).

Mesna: 50mg/day x 2 days will be given IV over 24 hours

rATG 0.5 mg/kg given on day –5, then 1.0 mg/kg given on day –4, then 1.5 mg/kg given on days –3 through –1. r ATG is infused over 10 hours. Premedicate with Acetaminophen 650 mg po and Diphenhydramine 25 mg po/IV 30 minutes before the infusion.

Rituxan (Rituximab) – The dose of 500 mg of Rituximab will be diluted in 500 ml 0.9 % NS and infused per standard Rituximab infusion guidelines, given on days –6 and on day + 1. Following the guidelines, Rituximab will be started at 50 mg/hr. If no reaction occurs, the dose will be increased by 50 mg/hr every 30 minutes to a maximum of 400 mg/hr.

G-CSF – guidelines, 5-10 mcg/kg/day will be started day + 5 and continued until the absolute neutrophil counts reaches at least 1,000/μl.

Plasmapheresis-In an autoimmune disease, the immune system attacks the body's own tissues. In many autoimmune diseases, the chief weapons of attack are antibodies, proteins that circulate in the bloodstream until they meet and bind with the target tissue. Once bound, they impair the functions of the target, and signal other immune components to respond as well.
Plasmapheresis is used to remove antibodies from the bloodstream, thereby preventing them from attacking their targets. It does not directly affect the immune system's ability to make more antibodies, and therefore may only offer temporary benefit. Neurologic diseases comprise 90% of the diseases that could profit from plasmapheresis.

Patients with clotting disorders may not be suitable candidates for plasmapheresis.

The basic procedure consists of removal of blood, separation of blood cells from plasma, and return of these blood cells to the body's circulation, diluted with fresh plasma or a substitute. Because of concerns over viral infection and allergic reaction, fresh plasma is not routinely used. Instead, the most common substitute is saline solution with sterilized human albumin protein. During the course of a single session, two to three liters of plasma is removed and replaced.
Plasmapheresis requires insertion of a venous catheter, either in a limb or central vein. Central veins allow higher flow rates and are more convenient for repeat procedures, but are more often the site of complications, especially bacterial infection.
When blood is outside the body, it must be treated to prevent it from clotting. While most of the anticlotting agent is removed from the blood during treatment, some is returned to the patient. To reduce this tendency citrate binds to calcium in the blood, calcium being essential for blood to clot. Citrate is very effective in preventing blood from clotting; however, its use can lead to life threatening low calcium levels. To prevent this complication, calcium is infused intravenously while the patient is undergoing the plasmapheresis; in addition, calcium supplementation by mouth may also be given.

Three procedures are available:

- "Discontinuous flow centrifugation." Only one venous catheter line is required. Approximately 300 ml of blood is removed at a time and centrifuged to separate plasma from blood cells.
- "Continuous flow centrifugation." Two venous lines are used. This method requires slightly less blood volume to be out of the body at any one time.
- "Plasma filtration." Two venous lines are used. The plasma is filtered using standard hemodialysis equipment. It requires less than 100 ml of blood to be outside the body at one time.

A single plasmapheresis session may be effective, although it is more common to have several sessions per week over the course of two weeks or more. In this case, plasmapheresis is performed at once before transplant to remove antibodies that will cause flare upon engraftment.

Aftercare

The patient may experience dizziness, nausea, numbness, tingling, or lightheadedness during or after the procedure. These effects usually pass quickly, allowing the patient to return to normal activities the same day.

Risks

Reinfusion (replacement) with human plasma may cause anaphylaxis, a life threatening allergic reaction. All procedures may cause a mild allergic reaction, leading to fever, chills, and rash. Bacterial infection is a risk, especially when a central venous catheter is used. Reaction to the citrate anticoagulant used may cause cramps and numbness, though these usually resolve on their own. Patients with impaired kidney function may require drug treatment for the effects of citrate metabolism.

Plasma contains clotting agents, chemicals that allow the blood to coagulate into a solid clot. Plasma exchange removes these. Bleeding complications are rare following plasmapheresis, but may require replacement of clotting factors (79).

6.4 Concurrent Treatment and Supportive Care Guidelines

6.4.1 Transfusion Support Guidelines

All blood products are to be irradiated (25 Gy). CMV negative patients are to receive CMV negative blood products or alternatively (leukocyte-poor) leukofiltered blood products. Prior to administration of blood products, patients may be medicated with Benadryl 10 - 25 mg IV or po and acetaminophen 650 mg po to prevent febrile reactions.

Red cells: For Hgb < 8.0 g/dl (Hct >27) transfuse 2 units irradiated ABO/Rh matched units.

Platelets: Platelets (irradiated) are given electively for platelet count less than 20 x 10^9/l. For procedures associated with a high risk of hemorrhage, including major surgical procedures, deep tissue biopsies, lumbar puncture, placement of central vascular catheter and endoscopy of the gastrointestinal tract, maintain platelet counts greater than 50 x 10^9/l. Platelets should be infused just before an invasive procedure. In addition to the platelet count, bleeding time, PT/PTT, fibrinogen and

other measures of coagulation may be helpful in some patients for defining the extent of any clotting dysfunction.

6.4.2 Infection Prophylaxis and Treatment Guidelines

All prophylactic antibiotics may be changed or discontinued according to clinical circumstances (e.g., patient allergy) as determined by the attending physician(s).

Antibacterial Prophylaxis: When neutropenia (neutrophils < 0.5 x 10^9/L) occurs, prior to the development of first fever, prophylactic antibiotics will be started. Cefepime 2 grams every 8 hours or Zosyn 3.75 g IV every 4 hours is recommended. Administration of antibiotics will be done according to the institutional standard of practice of the participating center.

Antifungal Prophylaxis: Fluconazole 400 mg po daily from day of transplant until 6 months post-transplant.

Antiviral Prophylaxis: Valacyclovir or acyclovir will be administered for HSV and VZV prevention from day of transplant until 12 months post-transplant. Administration of antiviral agents will be according to the institutional standard of practice of the participating center. If there is no documented standard of practice, then administration of antibiotics will be done.

Pneumocystis carinii pneumonia (PCP) Prophylaxis: Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim) DS tablet po every Monday, Wednesday and Friday starting after engraftment (absolute neutrophil count >500/ul for 3 days) and continued for 12 months. If the patient experiences a side effect to Bactrim (e.g., rash), aerosolized pentamidine 300 mg inhaled q month for 12 months will be substituted.

7.0 HOSPITAL DISCHARGE GUIDELINES

1. Afebrile.
2. No parenteral feeding required.
3. Platelet transfusion requirement less than 3x/week.
4. Neutrophil count greater than 500/ul.
5. Patient or family member is able to provide care.
6. Arrangements for follow-up with BMT physician and primary physician.

8.0 SIDE EFFECTS

Risk of hematopoietic stem cell transplantation. The major hazard of this protocol is transplant-related morbidity and mortality. The marrow ablative regimen of cyclophosphamide will destroy the patient's immune/hematopoietic system and leave the patient susceptible to a wide variety of infections and bleeding complications until the reinfused stem cells engraft. Aggressive supportive care as described above will be used to prevent all avoidable risk. However, a small percentage of patients may die as a direct result of transplant related complications. Transplant related mortality is directly related to a patient's age, general medical condition, and prior exposure to prolonged or aggressive chemotherapy regimens. Transplant related complications include infections,

bleeding, venom-occlusive disease of the liver, and failure to engraft. This protocol is designed to minimize these complications.

Risk of central line. Placement of an external central line catheter device is a routine procedure which may be done under local or general anesthesia. Potential complications include bleeding, pneumothorax, hemothorax, or arrhythmia. Like all artificial devices, lines may become infected and require treatment with antibiotics and/or removal.

Risk of lymphopheresis and leukapheresis. This procedure requires 4-6 hours (1-2 hours for lymphopheresis) and will be performed through apheresis catheter or a 16 gauge catheter introduced into the antecubital vein. The total volume outside the body at any time does not exceed 450 ml. The most common complication is hypocalcemia arising from citrate anticoagulation, which is usually mild or rarely severe with nausea, vomiting or arrhythmias. Symptoms are avoided with replacement solutions added during apheresis, slowing the flow rate, and/or supplemental oral antacids containing calcium. Other complications are infrequent, but include hypotension, vasovagal syncope, and infection.

Drug/chemotherapy side effects. See Section 9 - Drug Information.

9.0 DRUG INFORMATION

9.1 Cyclophosphamide

1. Other names: Cytoxan, Neosar
2. Chemical: 2-bis (2-chloroethyl) amino tetrahydro-2H-1, 3, 2- oxazaphosphorine-2-oxide monohydrate.
3. Classification: Alkylating agent.
4. Action: Causes prevention of cell division by forming adducts with DNA.
5. Metabolism: Metabolized to active compounds by microsomal enzymes in the liver. Excreted by the kidney in both the original form and as metabolites.
6. Availability: 25 mg and 50 mg tablets (tablets cannot be split); 100 mg, 200 mg, 500 mg, 2000 mg vials Mead Johnson and Adria.
7. Storage: Stable at room temperature indefinitely before reconstitution. After reconstitution, stable for 6 days upon refrigeration or for 24 hours at room temperature.
8. Administration: Dissolved in 500 cc 0.9%NS and administered over 60 minutes IV. Must be aggressively hydrated before, during, and for 24 hours after cyclophosphamide. If the rate of required hydration is not tolerated in a patient, bladder irrigation may need to be substituted.
9. Side effects: Myelosuppression, leukopenia (nadir 8-14 days), hemorrhagic cystitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), bladder carcinoma, cellular dysplasias, mucositis, rash, alopecia, anorexia, nausea, vomiting, sterile phlebitis, rare pulmonary toxicity, teratogenicity, hemorrhage, myocarditis, infertility, secondary leukemia; with rapid IV push, oropharyngeal tingling, metallic taste, headache, urticaria, facial swelling. Metabolic abnormalities following cyclophosphamide induced cell lysis can require dialysis in patients with underlying renal insufficiency.

9.2 G-CSF

1. Other name: Neupogen.
2. Description: Hematopoietic growth factor.
3. Drug administration: Subcutaneous administration 5-15mcg/kg/day.
4. Storage and Stability: 300 mcg and 480 mcg vials stored in refrigerator.
5. Toxicity: Myalgias, headache, flu-like symptoms, fever, bone pain in approximately 20% of patients, possible elevation of uric acid, transaminases, and LDH.

9.3 ATG Rabbit

1. Other names: thymoglobulin

2. Description: A rabbit polyclonal antibody to lymphocytes.

3. Drug administration – 2.0 mg/kg in D5W or NS infused over 10 hours.

4. Storage and Stability- 50mg/ml (5 ml ampule) vial stored in refrigerator.

5. Toxicity- Side effects of ATG are serum sickness and/or anaphylaxis: chills, arthralgias, headache, myalgia, nausea, vomiting, diarrhea, chest-pain, hypotension, dyspnea, pulmonary edema, abdominal pain. Other side effects in include abnormal liver function test (SGOT, SGPT) and renal function and thrombocytopenia.

9.4 Rituximab

1. Other names: Rituxan

2. Description : Biologic response modifier

3. Action: chimeric murine/human monoclonal antibody to the CD20 molecule on B-lymphocytes, the molecule is combined with Fc fragment of human IgG 1 kappa immunoglobulin containing murine light-and heavy-chain variable region sequence and human constant region sequences. Exact mechanism of action is unknown.

4. Availability: 10 mg/ml (10 ml and 50 ml ampules)

5. Storage: protected from light at 2-8 degrees centigrade.

6. Administration: patients should be premedicated with 25 mg Diphenhydramine and 650 mg of Acetaminophen 30 minutes prior to each Rituximab infusion. The dose of 500 mg of Rituximab will be diluted in 500 ml of 0.9 % NS and infused per standard Rituximab infusion guidelines (start at 50 mg/hour. If no reaction occurs, increase by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour).

7. Side effects: the most serious adverse reactions include infusion reactions, mucocutaneous reactions, hypersensitivity reactions, cardiac arrhythmias and angina, and renal failure. The infusion reactions can be treated by slowing or stopping the infusion and supportive care (Diphenhydramine, Acetaminophen, IV saline or vasopressors). Other reactions include: nausea/vomiting/diarrhea, headache, myalgias, arthralgias, cough, rhinitis, bronchospasm, dyspnea, sinusitis, lymphopenia, leucopenia, neutropenia, thrombocytopenia, anemia, abdominal pain, back pain, throat irritation, asthenia, infection. Reactivation of hepatitis B virus and progression to fulminant hepatitis has been reported in patients with negative hepatitis B surface antigen, but positive hepatitis B surface antibody.

10.0 Evaluation of toxicity

Daily assessment will be made with regards to toxicity by one of the protocol investigators. Common Toxicity Criteria Scale will be used to grade all non-hematologic toxicities.

11.0 Adverse event reporting

Any serious unexpected event **or** any death during the study, regardless of the cause, must be immediately reported to Richard K. Burt (312-695-4960). The Toxicity Grading for adverse events is according to NCI common toxicity criteria for adverse events (CTCAE) version 2.0 at website http:/ctep.info,nih.gov

11.1 To be reported by phone (312-695-4960) or FAX (312-695-4961) to Richard Burt:

a) All lethal (Grade 5) reactions. This information is to be immediately reported to Dr. Burt who will report it within 72 hours of a working day to the IRB and FDA.

11.2 To be reported in writing within 10 working days:

a) Grade 3 or 4 reactions, except myelosuppression which is anticipated. These will be reported by Dr. Burt on annual reports to the FDA

b) Any death within 30 days of study treatment, even if patient is off study.

12.0 Evaluation of response

To be performed at 6 months post-transplant, and then every year for 5 years.

13.0 Number of patients - 40, for phase I /II study.

14.0 Data Management

Collection of data, management, data checking and verification, will be performed by the PI and his team at Northwestern University Medical School. General Clinical Research Center statistician Dr. Jovanovic will be available to assist with data management and analysis. Analysis will be performed by the research staff using S-Plus, SAS and Microsoft Excel.

15.0 Statistical references

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16.0 Criteria for removal from study

1. Pregnancy prior to starting therapy.

2. Patient withdrawal - before beginning conditioning regimen or after successful recovery of hematopoiesis.

3. Disease progression making travel and follow-up studies of such inconvenience that they impose a significant risk or burden to the patient.

17.0 Follow- up procedures for withdrawal subjects

Unless the patient refuses, subjects who withdraw from the study will be followed in a manner consistent with the monitoring plan.

18.0 Stopping rules

Study will be held for any treatment –related death until reviewed and approved by the IRB, DSMB, and the US FDA. A treatment related death is any death deemed possibly, probably, or definitely related to therapy.

Disease relapse or progression will not be defined as toxicity but disease progression or relapse in greater than 5 of 10 patients having return of active Devic's within 1 year of treatment will also trigger stopping of the study until reviewed by IRB, FDA, and DSMB. Triggering of stopping rules will prompt cessation of new enrollment, notification of the IRB and FDA and performance of a comprehensive safety review.

19.0 Records to be kept

Records will be kept in the office of the Division of Immunotherapy.

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Appendix I

Muscle strength testing scale MRC - Scale

0: total lack of voluntary contraction
1: trace - faint contraction without any movement
2: poor - contraction with very weak movement through full range of movement, when gravity is eliminated.
3: fair - contraction with movement through the complete joint, range against gravity.
4: good - contraction with full range of movement against gravity and some resistance.
5: normal - contraction with normal strength through full range of motion against full resistance.

Appendix II

KURTZKE EDSS - Extended Disability Status Scale (EDSS) (41)

0= Normal neurological exam (all grade 0 in Function Systems (FS); Cerebral grade 1 acceptable).

1.0= No disability, minimal signs in one FS (i.e., grade 1 excluding Cerebral grade1).

1.5= No disability minimal signs in more than one S (more than one grade 1 excluding Cerebral grade 1).

2.0= Minimal disability in one FS (one FS grade 2, other 0 or 1).

2.5= Minimal disability in two FS (two FS grade 2, other 0 or 1).

3.0= Moderate disability in one FS (one FS grade 3, other 0 or 1), or mild disability in three or four FS (three/four FS grade 2, other 0 or 1) though fully ambulatory.

3.5= Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or Five FS grade 2 (others 0 or 1).

4.0= Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 500 meters.

4.5= Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest for some 300 meters.

5.0= Ambulatory without aid or rest for about 200 meters; disability sever enough to impair full daily activities (e.g. to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)

5.5= Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those for step 4.0).

6.0= Intermittent or unilateral constant assistance (cane, crutch or brace) required to walk about 100 meters with or without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).

6.5= Constant bilateral assistance (cane, crutch, or brace) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+).

7.0= Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair, wheels self in standard wheelchair and transfers alone; up and about in w/c some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone).

7.5= Unable to take more than a few steps; restricted to wheelchair, may need aid in transfer, wheels self but cannot carryon in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+).

8.0= Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems).

8.5= Essentially restricted to bed much of the day; has some effective use of arm (s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems).

9.0= Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+).

9.5= Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+).

10.0= Death due to MS

FUNCTIONAL SYSTEMS

Pyramidal functions

0= Normal

1= Abnormal signs without disability

2= Minimal disability

3= Mild or moderate paraparesis or hemiparesis; severe monoparesis

4= Marked paraparesis or hemiparesis; moderate quadriparesis; or monoplegia

5= Paraplegia, hemiplegia, or marked quadriparesis

6= Quadriplegia

V= Unknown

Cerebellar Functions

0= Normal

1= Abnormal signs without disability

2= Mild ataxia

3= Moderate truncal or limb ataxie

4= Severe ataxia; all limbs

5= Unable to perform coordinated movements due to ataxia

V= Unknown

X= Is used throughout after each number when weakness (grade 3 or more on pyramidal) interferes with testing.

Brain Stem Functions

0= Normal

1= Signs only

2= Moderate nystagmus or other mild disability

3= Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves

4= Marked dysarthria or other marked disability

5= Inability to swallow or speak

V= Unknown

Sensory Functions

0= Normal

1= Vibration or figure-writing decrease only, in one or two limbs

2= Mild decrease in touch or pain or position sense and/or moderate decrease in vibration in one or two limbs; or vibratory (c/s figure writing) decrease alone in three or four limbs.

3= Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs.

4= Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs

5= Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head

6= Sensation essentially lost below the head

V= Unknown

Bowel and Bladder Functions

0= Normal

1= Mild urinary hesitancy, urgency, or retention

2= Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence

3= Frequent urinary incontinence

4= In need of almost constant catheterization

5= Loss of bladder function

6= Loss of bowel and bladder function

V= Unknown

Visual (or Optic) Functions

0= Normal

1= Scotoma with visual acuity (corrected) better than 20/30

2= Worse eye with scotoma with maximal visual acuity (corrected) or 20/30 to 20/59

3= Worse eye with large scotoma, or moderate decrease in fields, but with maximal visual acuity (corrected) of 20/60 to 20/99

4= Worse eye with marked decrease of fields and maximal visual acuity (corrected) of 20/100 to 20/200; grade 3 plus maximal acuity of better eye of 20/60 or less

5= Worse eye with maximal visual acuity (corrected) less than 20/200; grade 4 plus maximal acuity of better eye of 20/60 or less

6= Grade 5 plus maximal visual acuity of better eye of 20/60 or less

V= Unknown

X= Is added to grades 0 to 6 for presence of temporal pallor

Cerebral (or Mental) Functions

0= Normal

1= Mood alteration only (Does not affect DSS score)

2= Mild decrease in mentation

3= Moderate decrease in mentation

4= Marked decrease in mentation (chronic brain syndrome – moderate)

5= Dementia or chronic brain syndrome – severe or incompetent

V= Unknown

Other Functions

0= None

1= Any other neurologic findings attributed to MS (specify)

V= Unknown

EDSS WORKSHEET

Date											
Pyramidal											
Cerebellar											
Brainstem											
Sensory											
Bowel/Bladder											
Visual											
Mental											
Other											
EDSS											

Appendix III

SCRIPPS NEUROLOGICAL RATING SCALE (NRS) WORKSHEET*

SYSTEMS EXAMINED	MAXIMUM POINTS	NORMAL	DEGREE OF IMPAIRMENT		
			MILD	MOD.	SEVERE
Mentation and Mood	10	10	7	4	0
Cranial Nerves:	21				
Visual Acuity		5	3	1	0
Fields, Discs, Pupils		6	4	2	0
Eye Movements		5	3	1	0
Nystagmus*		5	3	1	0
Lower Cranial Nerves	5	5	3	1	0
Motor:	20				
RU		5	3	1	0
LU		5	3	1	0
RL		5	3	1	0
LL		5	3	1	0
DTRS:	8				
UE		4	3	1	0
LE		4	3	1	0
Babinski: R:L (2 ea)	4	4	-	-	0
Sensory:	12				
RU		3	2	1	0
LU		3	2	1	0
RL		3	2	1	0
LL		3	2	1	0
Cerebellar:	10				
UE		5	3	1	0
LE		5	3	1	0
Gait: Trunk & Balance	10	10	7	4	0
Special Category: Bladder/Bowel/Sexual Dysfunction	0	0	-3	-7	-10
TOTALS	100				

*Points assigned for each component of the neurologic examination are subtotaled and points for autonomic dysfunction are subtracted leaving the final (NRS) score.

NEUROLOGICAL RATING SCALE SCORE: _____

Appendix IV

PASAT

COGNITIVE FUNCTION: PASAT—FORM A

Subject ID Number | Site Code | Test Date: Day | Month | Year

PASAT – Form A

RATE #1 (3 sec.)

1–4 5	8 12	1 9	5 6	1 6	3 4	7 10	2 9	6 8	9 15
4 13	7 11	3 10	5 8	3 8	6 9	8 13	2 10	5 7	1 6
5 6	4 9	6 10	3 9	8 13	1 9	7 8	4 11	9 13	3 12
7 10	2 9	6 8	9 15	5 14	2 7	4 6	8 12	3 11	1 4
8 9	5 13	7 12	1 8	8 9	2 10	4 6	9 17	2 16	6 16
3 12	1 4	5 6	7 12	1 11	8 12	1 9	3 4	8 11	2 10

Total Correct (raw) ____

RATE #2 (2 sec.)

1–3 7	7 10	2 9	5 7	1 6	8 9	6 14	9 18	1 10	7 8
9 16	4 13	6 10	3 9	5 8	8 13	1 9	6 7	2 8	7 9
5 12	9 14	3 13	5 9	2 7	6 8	4 10	8 12	3 11	5 8
9 14	7 16	4 11	2 6	8 10	5 13	2 7	1 3	6 7	4 10
7 11	3 10	5 8	9 14	6 15	4 10	5 9	2 8	9 12	1 13
1 5	8 9	3 11	1 4	6 7	8 14	4 13	4 9	2 8	6 8

Total Correct (raw) ____

COGNITIVE FUNCTION: PASAT—FORM B

Subject ID Number | Clinic Code | Visit Date: Day | Month | Year

PASAT—Form B

RATE #1 (3 sec)

2+7 9	5 12	8 15	2 10	9 11	6 15	4 10	1 5	3 4	6 9
3 9	6 9	2 8	8 10	4 12	9 13	3 10	6 7	7 13	2 9
4 6	1 5	5 6	7 12	3 10	9 12	7 16	2 9	6 8	8 14
4 12	2 6	5 7	8 13	5 13	9 14	5 12	7 10	1 8	4 5
2 6	4 6	3 7	6 9	1 7	7 8	5 10	8 11	3 11	9 12
1 10	3 4	5 8	2 7	6 8	4 10	9 15	7 16	1 8	4 5

Total Correct (max) = ___

RATE #2 (2 sec)

7+8 15	6 14	3 9	7 10	5 12	9 14	1 10	2 3	6 8	8 14
3 11	6 9	2 8	8 7	9 13	7 16	1 8	8 9	5 11	6 9
7 13	4 11	2 6	5 7	3 8	8 11	6 14	2 8	3 5	7 10
3 10	5 8	2 7	8 10	5 13	3 8	7 10	4 11	1 5	5 6
2 7	3 6	1 5	6 7	3 9	9 12	7 16	1 8	8 9	4 12
6 10	2 8	5 7	8 13	1 9	9 10	7 16	2 9	8 10	3 11

Total Correct (max) = ___

COGNITIVE FUNCTION: PASAT SUMMARY SCORE SHEET

Subject ID Number | Visit Date: Day Month Year

PASAT Summary Score Sheet

FORM USED (Check one) ☐ Form A ☐ Form B

PASAT 3"	**Value**	**Range**
Total Correct		0-60

For a completed PASAT 3", record any circumstances that affected the patient's performance

If PASAT 3" was not completed *(mark one)*: Specify

1. Unable to complete trial due to physical limitations →
2. Other →

PASAT 2"	**Value**	**Range**
Total Correct		0-40

For a completed PASAT 2", record any circumstances that affected the patient's performance

If PASAT 2" was not completed *(mark one)*: Specify

1. Unable to complete trial due to physical limitations →
2. Other →

Did it take more than one attempt to get one successful trial? ☐ Yes ☐ No
If yes, please specify reason(s) for more than one attempted trial:

Supplemental scores (optional)

PASAT 3"		**PASAT 2"**	
Total correct in first half		Total correct in first half	
Total correct in second half		Total correct in second half	
Total commission errors		Total commission errors	
Total omission errors		Total omission errors	

Appendix V

SF-36

Name_____

Date of Transplant_____

Visit Date _____

Short Form- 36 Health Survey (SF-36)

INSTRUCTIONS: The survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. **In general, would you say your health is:** (circle one)

a. Excellent 1

b. Very Good 2

c. Good 3

d. Fair 4

e. Poor 5

2. **COMPARED TO ONE YEAR AGO, how would you rate your health in general NOW?**

a. Much better now than one year ago 1

b. Somewhat better now than one year ago 2

c. About the same as one year ago 3

d. Somewhat worse now than one year ago 4

e. Much worse now than one year ago 5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Circle one number on each item

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	1	2	3
c. Lifting or carrying groceries.	1	2	3
d. Climbing several flights of stairs.	1	2	3
e. Climbing one flight of stairs.	1	2	3
f. Bending, kneeling, or stooping.	1	2	3
g. Walking more than a mile.	1	2	3
h. Walking several blocks.	1	2	3
i. Walking one block.	1	2	3
j. Bathing or dressing yourself.	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Circle one number on each line

	YES	NO
a. Cut down on the amount of time you spent on work or other activities.	1	2
b. Accomplished less than you would like.	1	2
c. Were limited in the kind of work or other activities.	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort).	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Circle one number on each line.

	YES	NO
a. Cut down on the amount of time you spent on work or other activities.	1	2
b. Accomplished less than you would like.	1	2
c. Don't do work or other activities as carefully as usual.	1	2

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

   Circle one

   a. Not at all 1

   b. Slightly 2

   c. Moderately 3

   d. Quite a bit 4

   e. Extremely 5

7. **How much bodily pain have you had during the past 4 weeks?**

   Circle one

   a. None 1

   b. Very mild 2

   c. Mild 3

   d. Moderate 4

   e. Severe 5

   f. Very Severe 6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Circle one

a. Not at all 1

b. Slightly 2

c. Moderately 3

d. Quite a bit 4

e. Extremely 5

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.**

How much of the time during the past 4weeks --

(circle one)	All of the Time	Most of the Time	A Good Bit of Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the *past 4 weeks,* how much of the time has your *physical health or emotional problems* interfered with your social activities (like visiting friends, relatives, etc.)?

Circle one

a. All of the time 1
b. Most of the time 2
c. Some of the time 3
d. A little of the time 4
e. None of the time 5

11. How TRUE or FALSE is *each* of the following statements for you?

(Circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier	1	2	3	4	5
b. than other people.					
c. I am healthy as anybody I know.	1	2	3	4	5
d. I expect my health to get worse.	1	2	3	4	5
e. My health is excellent.	1	2	3	4	5

Patient's initials: Date:

I confirm that the information on this survey is accurate. _____ _____

Staff initials: Date:

_____ _____

Appendix VI

FACT BMT

DATE OF BMT:

DATE FORM COMPLETED: M M D D Y Y Y Y

PERSON COMPLETING FORM:

FACT – BMT (VERSION 3)

Below is a list of statements that other people with your illness have said are important. By circling one number per line, please indicate how true each statement has been for you *during the past 7 days.*

PHYSICAL WELL-BEING

During the past 7 days:	Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
1. I have a lack of energy	0	1	2	3	4
2. I have nausea	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4. I have pain	0	1	2	3	4
5. I am bothered by side effects of treatment	0	1	2	3	4
6. I feel sick	0	1	2	3	4
7. I am forced to spend time in bed	0	1	2	3	4

8. Looking at the above 7 questions, how much would you say your **PHYSICAL WELL-BEING** affects your quality of life? (Circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all **Very much so**

SOCIAL/FAMILY WELL-BEING

During the past 7 days: Very at All	Not Bit	A Little what	Some- a Bit	Quite Much	
9. I feel distant from my friends	0	1	2	3	4
10. I get emotional support from my family	0	1	2	3	4
11. I get support from my friends and neighbors	0	1	2	3	4
12. My family has accepted my illness	0	1	2	3	4
13. Family communication about my illness is poor	0	1	2	3	4
14. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15. Have you been sexually active during the past year? D No D Yes					
If "Yes": I am satisfied with my sex life	0	1	2	3	4

16. Looking at the above 7 questions, how much would you say your **SOCIAL/FAMILY WELL-BEING** affects your quality of life? (Circle one number)

0 1 2 3 4 5 6 7 8 9 10
Not at all **Very much so**

RELATIONSHIP WITH DOCTOR

During the past 7 days:	Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
17. I have confidence in my doctor(s)	0	1	2	3	4
18. My doctor is available to answer my questions	0	1	2	3	4

19. Looking at the above 2 questions, how much would you say your **RELATIONSHIP WITH THE DOCTOR** affects your quality of life? (Circle one number)

0 1 2 3 4 5 6 7 8 9 10

Not at all **Very much so**

EMOTIONAL WELL-BEING

During the past 7 days:	Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
20. I feel sad	0	1	2	3	4
21. I am proud of how I'm coping with my illness	0	1	2	3	4
22. I am losing hope in the fight against my illness	0	1	2	3	4
23. I feel nervous	0	1	2	3	4
24. I worry about dying	0	1	2	3	4
25. I worry that my condition will get worse	0	1	2	3	4

26. Looking at the above 6 questions, how much would you say your **EMOTIONAL WELL-BEING** affects your quality of life? (Circle one number)

0 1 2 3 4 5 6 7 8 9 10

Not at all **Very much so**

FUNCTIONAL WELL-BEING

During the past 7 days:	Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
27. I am able to work (include work in home)	0	1	2	3	4
28. My work (include work in home) is fulfilling	0	1	2	3	4
29. I am able to enjoy life	0	1	2	3	4
30. I have accepted my illness	0	1	2	3	4
31. I am sleeping well	0	1	2	3	4
32. I am enjoying the things I usually do for fun	0	1	2	3	4
33. I am content with the quality of my life right now	0	1	2	3	4

34. Looking at the above 7 questions, how much would you say your **FUNCTIONAL WELL-BEING** affects your quality of life? (Circle one number)

0 1 2 3 4 5 6 7 8 9 10

Not at all **Very much so**

ADDITIONAL CONCERNS

During the past 7 days:	Not at All	A Little Bit	Some-what	Quite a Bit	Very Much
35. I am concerned about keeping my job (Include work in home)	0	1	2	3	4
36. I feel distant from other people	0	1	2	3	4
37. I worry that the transplant will not work	0	1	2	3	4
38. The effects of treatment are worse than I had imagined	0	1	2	3	4
39. I have a good appetite	0	1	2	3	4
40. I like the appearance of my body	0	1	2	3	4
41. I am able to get around by myself	0	1	2	3	4
42. I get tired easily	0	1	2	3	4
43. I am interested in having sex	0	1	2	3	4
44. I have concerns about my ability to have children	0	1	2	3	4
45. I have confidence in my nurse(s)	0	1	2	3	4
46. I regret having the bone marrow transplant	0	1	2	3	4

47. Looking at the above 12 questions, how much would you say your **ADDITIONAL CONCERNS** affects your quality of life? (Circle one number)

0 1 2 3 4 5 6 7 8 9 10

Not at all **Very much so**