Non-myeloablative Hematopoietic Stem Cell Transplantation for Stiff Person Syndrome (SPS) and Anti-GAD Antibody Variants: Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM), and Adult Onset Autoimmune Anti-GAD Positive Cerebellar Ataxia

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1.0 PRECIS

Stiff Person Syndrome is a chronic disease manifest by truncal and limb rigidity and spasms that affects the extremities, back, abdomen, and respiratory muscles. SPS is an autoimmune disease associated with high titer anti-glutamic acid decarboxylase (anti-GAD) antibodies that prevent inhibitory pathway relaxation of antagonists muscles groups. Painful spasms and rigidity result from excessive and prolonged motor neuron firing. Despite symptomatic and immunotherapeutic treatments, the disease is progressive and most patients require assistance for ambulation (cane, walker, wheelchair), develop postural deformities, have chronic painful spasm, and are unable to continue employment.
Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM) is a part of the SPS spectrum with anti-GAD antibodies limb and truncal rigidity, muscle
spasm, brain stem signs (gaze palsies, facial weakness, ptosis etc), and hyperekplexia (pronounced startle responses to tactile or acoustic stimuli) . Although rare, anti-GAD positive cerebellar ataxia without known spinal cerebellar atrophy mutations is also considered a variant of SPS. Based on our encouraging results of non-myeloablative hematopoietic stem cell transplantation, for patients with multiple sclerosis and chronic inflammatory demyelinating polyneuropathy, we will investigate the role of non-myeloablative hematopoietic stem cell transplantation for patients with SPS who require assistance to ambulate.

2.1 OBJECTIVES

We will assess the toxicity/efficacy (phase I/II) of cyclophosphamide, anti-thymocyte globulin and rituxan with autologous hematopoietic stem cell transplantation for SPS. There are no established criteria for complete remission (CR) or partial remission (PR). The primary (survival) and secondary (disease improvement) endpoints to be considered in this study are:

2.2 Primary end point – Overall Survival
2.3 Secondary endpoint **--** Disease improvement

- Decrease (50%) and complete discontinuation of muscle relaxation anti-spasmotic medications
- Chronic Pain acceptance questionnaire (CPAQ) (appendix I)
- Timed ambulation
- Activities of Daily Living (appendix II)
- SF-36 QOL (Appendix III)
- Rankin Functional Scale (appendix IV) (Improvement for disability scales is defined in the same manner as for the SF-36 QOL, that is whether or not there is a statistically significant change in the score / scale / dimension done by standard statistical methodology such as student t test or mixed method analysis.

3.0 BACKGROUND – STIFF PERSON SYNDROME

Glutamic acid decarboxylase (GAD-65) catalyses glutamate conversion into γ-aminobutyric acid (GABA) in the central nervous system and in the pancreatic β cells (1, 2). Neurons that produce *GABA* have predominately inhibitory effects on neuronal firing. Antibodies targeting GAD-65 occur in stiff person syndrome, cerebellar ataxia, epilepsy, limbic encephalitis, combinations thereof, and diabetes mellitus (3, 4). While patients with type I diabetes generally have low titer antibodies to GAD-65, patients with SPS may have high titer antibodies against GAD-65 (5, 6). However anti-GAD antibodies are insufficient to make the diagnosis and only 60-80% of SPS patients have anti-GAD antibodies (6, 7). Possible etiologies for SPS in patients without anti-GAD antibodies include antibodies to GABA-A receptor associated protein, synaptophysin, gephyrin, and GABA-transaminase (7-12). It may be that differences in recognition of presynaptic GAD epitopes or post synaptic pathways may explain the various manifestations, i.e. stiffness, spasms, rigidity, cerebellar ataxia (dysmetria, nystagmus, dysarthria, ataxia, oculomotor dysfunction), epilepsy, limbic encephalitis, diabetes, or combinations thereof (14-19).

Anti-GAD antibodies do not correlate with disease severity, diversity of symptomatology or response to therapies (20). Anti-GAD antibodies define a novel group of syndromes, collectively viewed as 'hyperexcitability disorders' but historically SPS is termed according to the most common manifestation as Stiff Person Syndrome (20). Other than an autoimmune etiology, Stiff Person Syndrome may have be a paraneoplastic manifestation of an underlying malignancy (20). Paraneoplastic SPS antibodies may be associated with antibodies to amphiphysin in patients with breast cancer or small cell lung cancer (21, 22)

Stiff Person Syndrome is rare with an incidence of 1 person per million and a 2; 1 female / male ratio (1, 23). There is no cure for Stiff person syndrome. No positive controlled clinical trials to establish standard optimal therapy have been reported. Current treatment consists of benzodiazepines (diazepam, clonazepam) intrathecal baclofen (24-27), anticonvulsants (28), and immune modulation with steroids (29), plasma exchange (30), IVIG (31-33), and rituximab (34). The natural history of Stiff Person Syndrome is axial, limb, and paraspinal muscle spasms leading to gait disability and progressive disability and inability to walk without assistance. Emotion stress, or unexpected sounds or touch can lead to a sudden attack (35). The fear of sudden unexpected attacks results in fear of leaving the house and being stranded if an attack occurs ultimately leading to loss of independence, assistance in ambulation, and inability to bend at the waist (36). Sudden death due to autonomic dysfunction (hyperpyrexia, diaphoresis, tachypnea, tachycardia, pupillary dilation, and arterial hypertension) may also occur (37).

4.1 DIAGNOSIS OF SPS

4.2 Differential clinical diagnosis for SPS (38)

- Myelopathy: compressive, ischaemic, haemorrhagic and inflammatory (including multiple sclerosis and infectious causes)
- Myopathy: channelopathies, inflammatory, myotonic dystrophy, paramyotonia
- Neuropathic: neuromyotonia, Isaac's syndrome
- Parkinson's disease or Parkinson-plus syndromes (e.g., progressive supranuclear palsy, multiple system atrophy)
- Primary lateral sclerosis
- Dystonia (generalised and focal)
- Ankylosing spondylitis
- Neuroleptic malignant syndrome, malignant hyperthermia and serotonin syndrome
- Tetanus
- Psychogenic
- Hereditary spastic paraparesis
- Leukodystrophies
- Drug-induced and toxicity: monoamine oxidase inhibitors, phenothiazines, amphetamines, 5,6-methylenedioxy-N-methyl-2-aminoindane, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, carbon monoxide
- Spinal interneuronitis with rigidity

4.3 Dalakas criteria for the diagnosis of typical stiff person syndrome (38-40)

- Stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscle leading to a fixed deformity (hyperlordosis)
- Superimposed painful spasms precipitated by unexpected noises, emotional stress, tactile stimuli
- Confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography
- Absence of neurological or cognitive impairments that could explain the stiffness
- Positive serology for GAD65 (or amphiphysin or other) autoantibodies, assessed by immunocytochemistry, western blot or radioimmunoassay
- Response to diazepam

5.1 RATIONALE AND SCIENTIFIC JUSTIFICATION:

"If we are uncritical we shall always find what we want: we shall look away from, and not see, whatever might be dangerous to our pet theories."—The Poverty of Historicism - Karl Popper

There are many misconceptions about hematopoietic stem cell transplant for autoimmune diseases.

First, generally speaking, conditioning may be non-myeloablative or myeloablative. Myeloablative regimens are based on myeloablative cancer drugs and/or total body irradiation. These extreme regimens cause irreversible bone marrow failure, thus requiring HSC reinfusion to recover. Toxicity, cost, and late complications (e.g., infertility, secondary myelodysplasia, leukemia, and solid tumors) can be substantial with this approach. In contrast, non-myeloablative regimens (as we use herein) are designed to maximally suppress the immune system without destruction of the bone marrow stem cell compartment.

Second, when using a non-myeloablative regimen recovery occurs without infusion of stem cells and the stem cells are autologous. While not necessary for recovery, stem cell infusion may shorten the interval of neutropenia and attendant complications. Thus in reality there is no transplant only an autologous supportive blood product.

What follows is mostly unpublished data from our own experience in transplant of neurologic disease (MS and CIDP) in order to demonstrate the safety and efficacy of this type of treatment. Most of the following data is in the process of being written or already under peer review and needs to be treated as propriety and confidential.

EXPERIENCE OF NON-MYELOABLATIVE HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) FOR OTHER NEUROLOGIC AUTOIMMUNE DISEASES: MULTIPLE SCLEROSIS AND CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

5.2 MULTIPLE

SCLEROSIS Introduction

Multiple sclerosis (MS) is an immune mediated disorder of the central nervous system that in most patients begins as an inflammatory relapsing remitting (RR) disease. Subsequently and despite standard therapies, the majority of patients eventually enter a secondary progressive (SP) phase for which no therapy has demonstrated efficacy. Fifty percent of patients are unable to continue employment, require assistance to ambulate, or are unable to walk by 10, 15, and 25 years from diagnosis, respectively. Despite an annual cost of treating MS that is approximately $47,000 USD per patient (41, 42), no

FDA approved therapy has been demonstrated to significantly reverse neurologic disability or improve quality of life (43-49).

Between July 2003 and June 2013, 129 patients underwent HSCT for MS at Northwestern University (Chicago). Three patients who remain alive (by phone contact) are not included in the analysis because two failed to return for neurologic evaluation and one had inconsistent neurologic findings. The remaining 126 patients returned for follow- up and are included in this analysis. All patients were treated at Northwestern University (Chicago, Illinois, USA) on either an Institutional Review Board (IRB) approved study (n=50) or on a compassionate basis (n=76). Patients treated on a compassionate basis signed consent forms and were treated and followed before and after transplant in an identical manner to those on study and are reported with retrospective IRB approval.

The reasons and number of patients treated on a compassionate basis were: entering SPMS (n=22), insurance refused coverage (n=15), a single prior brainstem or visual relapse or cognitive impairment such that further attacks or disease progression would be deemed to render them para- or quadriplegic, blind, cognitively impaired, or unable to continue employment (n=14), EDSS greater than 6.0 (n=10), failed all available FDA approved treatments (n=8), other coexisting autoimmune or neurologic diseases (n=4) and one each for age over 55, allergy to gadolinium, and tumefactive MS.

Study end points
The primary end-points were safety, relapse-free survival (no acute relapses), progression free survival (no increase in EDSS) and event free survival (no acute relapses, no progression and no new gadolinium enhancing or T 2 lesions on MRI). Secondary endpoints were disability and impairment defined by the EDSS and NRS scores. Tertiary endpoints consisted of the MSFC, quality of life short-form 36 (SF-36) questionnaire, and MRI enhancing and total brain T2 lesion volume (T2LV).

Results

Demographics
All patients were followed from 6 months to 5 years (mean 32 months). The patients' median age was 36 years (range 18 to 58 years old), with a female to male ratio of 1.4, and predominately Caucasian ethnic origin (107 Caucasian, 9 African American, 6 Asian, and 4 Hispanic). The mean duration of disease from time of diagnosis was 79 months (range 9 to 264 months). Mean EDSS was 4.05 (range 1.5 to 8).

Engraftment and toxicity
After stem cell infusion, the median day of white blood cell engraftment (absolute neutrophil count > 1000 / ul) and hospital discharge were day 9 and 10, respectively. The mean number of platelet and red blood cell transfusions were 2.6 and 2.1, respectively.

Admission rectal surveillance cultures were positive for vancomycin resistant enterococcus in 12 patients, while admission nasal cultures were positive for methicillin- resistant *Staphylococcus aureus* (MRSA) in 2 subjects. Fever > 38^{0} Celsius (100.4 Fahrenheit) occurred in 63 patients (50%) all of whom were blood culture negative except one who had coagulase-negative staphylococcus thought to be a

contaminant. Diarrhea positive for *Clostridium difficile* occurred in four patients.

There was no treatment related mortality and no early or late fungal, *Pneumocystis jirovecii*, cytomegalovirus, Epstein Barr, or JC virus infections. Four patients developed late reactivation of dermatomal zoster treated with oral acyclovir. Immune-mediated thrombocytopenia (ITP) developed in (3 of 17) (17%) patients treated with alemtuzumab compared to 2 of 109 (1.8%) patients treated with ATG (P = 0.02). Drug free remission of ITP occurred in all cases after transient treatment with corticosteroids and intravenous immunoglobulin, and / or rituximab.

Hypothyroidism was present in seven patients (5.5%) before transplant. After transplant, seven additional patients developed thyroid abnormalities with hypothyroidism or hyperthyroidism occurring in 2 and 5 patients, respectively. For the 119 patients who did not have pre HSCT thyroid abnormalities, thyroid dysfunction subsequently developed in 14% (2 of 14) treated with alemtuzumab and 4.8% (5 of 105) treated with ATG (P = 0.19). No patient developed leukemia or myelodysplasia. During transplant hospitalization, one patient was incidentally found to have a pre-existing adrenal mass that upon resection was localized adrenal carcinoma. Three years after transplant, one patient developed breast ductal carcinoma in situ.

Overall survival, relapse free survival, progression free survival, disease activity free survival
Treatment related mortality was 0% and overall survival 99.2%. One death occurred 30 months after HSCT related to hypertensive cardiovascular disease. The Kaplan-Meier estimated 5-year relapse-free survival (no acute relapses), progression free survival (no increase in EDSS), and disease activity free survival (no acute relapses, no progression, and no new gadolinium enhancing or T 2 lesions on MRI) are 93%, 88%, and 78%, respectively.

EDSS and NRS
The EDSS and NRS scores improved significantly at all post-transplant evaluations (P<0.001). For all patients, the mean EDSS scores improved from 4.05 pre-transplant to 3.32 at 6 months, 3.1 at 12 months, 3.03 at 24 months, and then remained relatively stable with values at 36, 48, and 60 months of 3.12, 2.89, and 2.94, respectively. Similarly, the NRS scores improved from a mean pre-transplant value of 72.1 to post HSCT scores of 80.3, 81.9, and 83.8 at 6, 12 and 24 months, respectively, and thereafter remained relatively stable at 84.2, 84.7, and 83.1 at 36, 48, and 60 months, respectively.

On multivariate analysis, EDSS outcome was influenced by pre-transplant disease duration (P = 0.003) and clinical disease course (RR versus SP). NRS outcome was affected by pre-transplant disease duration, pre-transplant clinical disease course, and fever during transplant. Gender and age had no independent effect on EDSS or NRS scores.

MSFC
Based on comparison with the means and standard deviations from pre-HSCT baseline, the MSFC score and its component Z-scores for the 25-foot walk, 9-hole peg test, and PASAT 3 second improved significantly at 6, 12, 24, 36, 48, and 60 months after transplant.

MRI metrics
The number of enhancing lesions on brain MRI decreased significantly at all post-transplant time points. The percentage of patients with at least one enhancing lesion from 6 to 3 months before HSCT, within 3 months of HSCT, and at 6, 12, 24, 36, 48, and 60 months after transplant were 30%, 56%, 0.8%, 2%, 3.8%, 3.7%, 11%, and 8%, respectively. The mean number of enhancing lesions was 3.22 at 3 to 6 months before HSCT, 2.57 within 3 months of HSCT, 0.01 at 6 months, 0.13 at 12 months, 0.07 at 24 months, 0.24 at 36 months, 0.67 at 48 months, and 0.08 at 60 months post-transplant. Brain T2 lesion volume (T2LV) decreased significantly between pre transplant MRI scan and most recent post-transplant MRI scan. With a mean follow-up of 2.6 years, the mean T2LV decreased by 31% from 16.36 cm^3 (SD 18.65, median 8.8, range 84.5 – 0.23) to 11.32 cm^3 (SD 12.92, median 5.66, range 55.2-0.09) ($P < 0.0001$).

Quality of Life
Between pre-transplant and last evaluation, patients' quality of life as measured by the SF-36 improved significantly in all scales ($P \leq 0.002$) and dimensions ($P < 0.001$) and in total score ($P < 0.001$) .

Discussion of HSCT for MS

HSCT in patients with RRMS using a non-myeloablative immune-specific regimen and unselected peripheral blood stem cells had no treatment-related mortality and little infectious toxicity including no late opportunistic infections other than reactivation of dermatomal zoster. Specifically, there was no CMV-related disease or JC virus induced progressive multifocal encephalopathy (PML). To date, our results compare favorably with reports of natalizumab related PML (50) or fingolimod related cardiovascular events and herpes encephalomyelitis (51).

In patients with MS, this report shows that ITP is a significantly more frequent complication after treatment with a regimen containing alemtuzumab compared to ATG. This is consistent with an earlier report that alemtuzumab containing transplant regimens for autoimmune diseases are associated with an increased risk of immune mediated cytopenias independent of the autoimmune disorder being transplanted (52). However, thyroid dysfunction appears to be a relatively more unique complication of immune based therapies for MS. Without transplant, thyroid dysfunction has been reported to occur in 34% of patients treated with alemtuzumab and 6.5% of patients treated with interferon beta-1a (53). Of patients referred to us for HSCT, 5.5% already had thyroid dysfunction. Following HSCT with either alemtuzumab or ATG another 14% and 4.8%, respectively, developed thyroid dysfunction.

A correlation between T2 lesion load and EDSS progression has been demonstrated in RRMS, where change in lesion load in the first 5 years correlates with late EDSS disability (54). Herein, we demonstrate that a sustained improvement in EDSS scores following HSCT is accompanied by a decrease in MRI T2LV. Decreased T2LV may be related to resolution of inflammation and edema. However, the rate of lesion growth for RRMS has been reported to be on average+ 0.80 cm^3 / year, that is an expected increase of approximately +2.0 cm in 2.6 years (55). In comparison, during the same time interval, the mean T2LV in the transplant cohort decreased by -5.04 cm^3. In a similar manner, improvement in the MSFC score is consistent with improvement in EDSS (56).

Patient selection is important in determining outcome since the EDSS disability and NRS impairment scores did not improve in patients with SPMS or in those with disease duration longer than 10 years. These factors, in multivariate analysis, were independent prognostic variables. In our study, older age, *per se*, did not have a worse outcome although older patients with an established diagnosis of SPMS were excluded from transplant. Nevertheless our data suggest that older patients, if they still have inflammatory MS, improve after transplant.

Heat stress can affect neuron metabolism and brain function (57), and fever has been reported as an unfavorable prognostic factor for neurologic recovery in other types of neuronal injury such as cardiopulmonary bypass, cardiac arrest, cerebral vascular accidents, traumatic closed head injury, and subarachnoid hemorrhage (58-62). For MS, environmental heat is associated with pseudo-relapses and or severe fatigue (63, 64). In our study, maximum body temperature during transplant hospitalization correlated with higher EDSS scores (worse disability) in univariate but not multivariate analysis. Transplant fever and final neurologic outcome may be linked to the clinical course of MS and or disease duration since brain temperature has been reported to be higher in MS patients with higher disability (65). Unlike EDSS scores, the effect of fever was significant ($P < 0.05$) in multivariate analysis for post-transplant NRS impairment. This difference might be due to the fact that the EDSS and NRS are different outcome measures. EDSS is non-linear and biased towards locomotor function, while the NRS has a wider range of scores and is more sensitive to non-ambulatory changes in the clinical statues (66).

In this cohort of 126 MS patients, a non-myeloablative reduced intensity conditioning regimen followed by infusion of unselected autologous peripheral blood stem cells significantly improved neurologic disability and impairment (NRS and EDSS) as well as quality of life, MSFC, and T2 MRI lesion burden. HSCT using a non-myeloablative regimen should be considered in patients with frequent relapses.

5.2 CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune- mediated demyelinating disease of the peripheral nervous system that may present acutely or insidiously with either a progressive, stepwise, or relapsing clinical course (67). "Typical" CIDP as defined by the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) affects proximal and distal motor and sensory function, results in diminished deep tendon reflexes, and evolves over at least 2 months (68, 69). "Atypical" CIDP variants have heterogeneous phenotypic patterns that may be multifocal (Lewis-Sumner Syndrome), distally accentuated (distal acquired demyelinating symmetric or DADS), purely motor, or purely sensory (68, 69). The pathogenesis of CIDP and atypical variants has yet to be well characterized but is likely to involve multiple immune pathways that contribute to chronic neural dysfunction (70). Advances in our understanding of CIDP immunopathology have highlighted the importance of both T cells and antibodies (71), even though in the majority of CIDP patients the cryptic antigenic target(s) is unknown (70).

CIDP remains one of the few peripheral neuropathies for which effective therapy exists (72, 73). Corticosteroids (74, 75), intravenous immunoglobulin (IVIG) (76, 77), and plasmapheresis (78) have each been shown to be effective in randomized clinical trials. Retrospective studies have shown that when more than one of these conventional therapies are utilized approximately 80% of CIDP patients respond (79, 80). However, some individuals do not respond to first-line treatments (81), or become refractory or intolerant to conventional intervention (82). Furthermore, side effect profiles, quality of life restrictions, and financial burdens can limit the use of corticosteroids, intravenous immunoglobulins (IVIG), and plasma exchange (83- 85). These limitations are especially relevant when treatment is chronic, as is often the case in those with CIDP. Herein, we report the results of non-myeloablative hematopoietic stem cell transplantation (HSCT) for patients with CIDP refractory to conventional treatment options.

Methods

Patients

Patients were treated at Northwestern Memorial Hospital (Chicago, Illinois, USA) on an IRB and FDA approved protocol (www.clinicaltrials.gov NCT00278629). The trial was initially designed to include 40 patients but given the results herein has been extended to eighty patients and to allow longer follow-up. Eligible patients met European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS / EPS) electromyography (EMG) criteria for definite CIDP and failed corticosteroids and either IVIG or plasmapheresis. Failure was defined as persistent MRC grade 3/5 or worse weakness in at least one muscle or grade 4/5 in at least two muscles, or dysphagia, or persistent incapacitating sensory loss (e.g. gait ataxia). Patients dependent on IVIG or plasmapheresis had to be documented to deteriorate upon stopping or delaying

treatment or decreasing dose.

Patients were excluded if they had only possible or probable CIDP by EFNS/PNS criteria, or had other plausible explanations for neuropathy such as Charcot Marie Tooth neuropathy or a family history of neuropathy, drug or toxin exposure, Lyme disease, hepatitis or HIV, diabetes, plasma cell dyscrasias, hematologic malignancies, POEMS syndrome, amyloidosis, or presence of sphincter disturbances. Other presumed immune- mediated neuropathies that respond differently to standard immune based treatments such as Multifocal Motor Neuropathy (MMN), DADS with anti-MAG antibodies, or Chronic Ataxic Neuropathy, Ophthalmoplegia, Monoclonal IgM protein, cold Agglutinins and Disialosyl antibodies (CANOMAD) were excluded from this evaluation. Patients with MGUS underwent a skeletal survey and bone marrow biopsy and aspirate to rule out hematologic malignancies. General health exclusion criteria included age < 18 or > 65 years old, left ventricular ejection fraction < 40%, DLCO < 40%, creatinine > 2.0 mg/dl, or hepatic transaminases or bilirubin greater than twice normal. After initiation, the protocol was amended to exclude patients with history of cancer, poorly controlled hypertension, or hypertension related end organ dysfunction.

Results

One hundred and thirty patients were referred for HSCT. The majority, 90 patients, were not candidates because they did not meet EFNS/PNS criteria for definitive CIDP. After evaluation, the most common reason for exclusion was diagnosis of another neurologic disorder (n=35) including length dependent neuropathy (n=5), motor neuron disease (n=4), Charcot Marie Tooth genetic neuropathy (n=3), multifocal motor neuropathy (n=4), DADS with anti-MAG antibody (n=4), small fiber neuropathy (n=3), idiopathic neuropathy (n=2), and one each for multiple mononeuropathies, autoimmune autonomic ganglionopathy, Parsonage Turner syndrome, Wartenberg migrant sensory neuropathy, lumbosacral radiculopathy, chronic inflammatory sensory polyneuropathy (CISP), Guillaine Barre Syndrome (GBS), cauda equine syndrome, and CANOMAD.

The second largest group excluded from the study had possible or probable CIDP but were excluded because they did not meet EFNS/PNS criteria for definitive CIDP (n=24) or had received an inadequate trial of IVIG (n=5). Six patients had malignancies (plasmacytoma) (n=3), and one each for lymphoma, POEMS, and melanoma). Three patients were found to have myopathies: inclusion body myositis (n=2), limb-girdle syndrome (n=1).

Other reasons for exclusion included other confounding medical explanations for neuropathy (n=8) (diabetes (n=3), and one each of prior high dose chemotherapy, lumbosacral plexus radiation, coronary artery disease, osteomyelitis, and age > 65 years old), awaiting or denied insurance approval (n=10).

Demographics

Forty patients have been followed from 6 months to 5 years after transplant (mean 24 months). Two patients are alive but have not returned for follow-up. The patients' mean age was 44 years (range 20 to 63 years old), with a male to female ratio of 2.1 and predominately Caucasian ethnic origin (32 Caucasian, 4 Hispanic, 2 African American, 2 Asian). The mean duration of symptoms before undergoing HSCT was 91 months (range 14 to 360 months). Thirty-three patients had typical and 7 atypical CIDP. CIDP

presented as acute or insidious onset in 10 and 30 patients, respectively. Before HSCT all patient had received corticosteroids and IVIG and 20 patients (50%) had received plasmapheresis.

Safety / survival
There was no treatment related mortality. Overall survival is 95%, (38/40). One patient who had been treated for Hodgkin's lymphoma twenty-five years earlier and before transplant had symptoms of stomach outlet obstruction died 1 year after transplant from metastatic signet cell stomach cancer that originated within the prior mantle field radiation portal. A second patient with poorly controlled chronic hypertension-related cardiac and renal end organ dysfunction died from a sudden cardiovascular death 3 months after HSCT. Thereafter, enrollment criteria were tightened to exclude patients with comorbid diseases or any prior cancer. The mean red blood cell and platelet transfusions were 2.9 and 3.4, respectively. Before starting transplant rectal surveillance cultures were positive for vancomycin resistant enterococcus and extended-spectrum □- lactamase resistance in 3 and 4 patients, respectively. During hospitalization 33% (13/40) remained afebrile while 45% (18/40) and 23% (9/40) developed a maximum fever greater or equal to 38.5^{o}C and 39.0^{o}C, respectively. Two patients had blood cultures positive for coagulase negative *staphylococcus*. Two patients had positive urine cultures, one for *enterococcus faecalis*, and one for *escherichia coli*. No patient became septic or hypotensive. The mean day of discharge was day 11 after stem cell infusion.

There were no early or late post-transplant fungal, *Pneumocystis jirovecii*, cytomegalovirus, Epstein Barr, or JC virus infections. No patient has developed myelodysplasia or hematopoietic malignancies. One patient with an abnormal cervical pap smear declined medical intervention for more than 1 year. Subsequently, following surgery, radiation, and chemotherapy for cervical cancer, she has remained cancer free for 2 years.

Medication free
Eighty-three percent of patients were tapered off all immune modulating medications. Seventy-four percent (28/38) became medication free immediately after HSCT. Over 4 to 18 months, three patients were tapered off IVIG and 1 patient each was tapered off prednisone and mycophenylate mofetil. Four patients, all within 8 months of transplant, are currently undergoing a gradual taper of IVIG (3 patients) or plasmapheresis (1 patient). Three patients who became medication free immediately following HSCT restarted IVIG at 1, 2, and 4 years following transplant. The percent of patients free of any immune modulating therapy at 6 months and 1, 2, 3, and 4 years after transplant are 74%, 81%, 83%, 92%, and 75%, respectively (figure 1).

Outcome measures
The MRC improved significantly from 51.3 pre HSCT to 55 ($P<0.001$), 56.4 ($P<0.001$), 55.5 ($p=0.008$), 55 ($p=0.05$), and 55.5 ($p=0.04$) at 6, 12, 24, 36, and 48 months after HSCT. Rankin functional score improved from 2.92 pre HSCT to 2.04 ($p< 0.001$), 1.78 ($p= 0.002$), 1.9 ($p=0.03$), 1.75 ($p=0.05$), and 1.5 ($p=0.03$) at 6 months, 1, 2, 3, and 4 years. The Barthel Index improved from 83.2 pre HSCT to 94.5 ($p=0.003$), 96.6 ($p<0.001$), 96.7 ($p=0.03$), 96.3 ($p=0.04$), and 95.8 ($p=0.05$) at 6 months, 1, 2, 3, and 4 years. The INCAT disability scale was added after the study began and consequently has shorter follow-up but improved from a pre-transplant value of 4.47 to 3.05

(p<0.001), 1.67 (p<0.001), and 2.8 (p=0.004) at 6 months, and 1 and 2 years after HSCT.

Electrophysiology
Demyelination as measured by both conduction blocks (CB) and nerve conduction velocity (NCV) improved significantly following transplant. The mean percent CB improved from 36.11 pre transplant to 26.35 (p=0.005), 23.84 (p=0.001), 27.15 (p=0.18), 26.17 (p=0.01), and 10.6 (p=0.04) at 6 months and 1, 2, 3, and 4 years post HSCT. The number of nerves with greater than 50% CB was 1.18 pre HSCT compared to 0.61 (p=0.002), 0.41 (p=0.001), 0.58 (p=0.33), 0.36 (p=0.03), and 0.17 (P=0.10) at 6 months, 1, 2, 3, and 4 years after transplant. The average NCV (in m/s) improved from 24.82 pre- HSCT to 30.74 (p=0.001), 34.45 (p < 0.001), 34.35 (p=0.008), 36.77 (p=0.004), and 42 (p=0.001) at 6 months, 1, 2, 3, and 4 years post-transplant (figure 3). The NCV (in m/s) of the most severely affected nerve improved from 20.04 pre-HSCT to 26.37 (p=0.004), 28.9 (p<0.001), 28.13 (P=0.02), 30.65 (p=0.005), and 35.32 (p=0.001) at 6 months, 1, 2, 3, and 4 years post-transplant.

The average CMAP amplitude (in millivolts) improved from 3.18 pre-transplant to 3.66 (p=0.50), 4.55 (p=0.001), 4.3 (p=0.02), 4.99 (p=0.02), and 4.67 (p=0.02) at 6 months and 1, 2, 3, and 4 years after transplant. The CMAP (in millivolts) of the most severely affected nerve improved although not statistically significant from a pre-transplant mean of 0.64 to 0.79, 1.18, 1.16, 1.31, and 1.43 at 6 months, and 1, 2, 3, and 4 years after HSCT.

Quality of Life
Between pre-transplant and last evaluation, patients' quality of life as measured by the SF-36 improved significantly in all scales except emotional role limitation and mental health (table 2). There was significant improvement in both physical and mental dimensions (P< 0.001) and in total score (P < 0.001).

Discussion

Since the first report of HSCT for CIDP was published in 2002 (86) several case reports and small retrospective case series have followed (87-92). In the largest series, 8 of 11 patients with CIDP treated with HSCT were in drug free remission at the time of publication (median follow-up duration 28 months) (87). We prospectively evaluated the safety and efficacy of HSCT in a population of well- defined EFNS/PNS "definite" CIDP patients refractory to at least 2 of 3 conventional immunotherapy treatments. Similar to the smaller retrospective series (87), 66% received no additional immunotherapy after HSCT, and an additional 13% tapered off immunotherapy within 18 months of HSCT. These patients, comprising nearly 80% of the total cohort, were relapse-free for the duration of the available follow- up. Interval improvement in strength (MRC sum score), disability (Rankin functional score, Barthel index, INCAT), quality of life (SF-36), and electrophysiology evidence of demyelination (mean nerve conduction velocity, conduction velocity of most severely affected nerve, mean conduction block, and number of nerves with > 50% conduction block), and electrophysiology evidence of neuronal regeneration (mean CMAP) were concurrently observed to improve during the follow-up period.

From a clinical perspective, there are little long-term outcome data in CIDP using

conventional therapy. The landmark IVIG CIDP Efficacy (ICE) and pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT) trials reported 6 month drug free remission in 55% (ICE) and 40% (PREDICT) of patients (77, 93). A subsequent PREDICT analysis with a median follow up of 4.5 years revealed that only 26% of the initial cohort had a sustained remission (94). Similar to the follow-up PREDICT result, other retrospective series of IVIG (95) or heterogeneously (96) treated CIDP patients with at least 4 years of median follow have reported long term drug free remission in 25% and 31% of patients, respectively.

Our results with a median follow up of 24 months are thus far favorable to prior observations, especially since we selected IVIG and or plasmapheresis failures of whom only 7 (18%) relapsed after HSCT, while only 1 patient showed no definite improvement. When relapse occurred, most (5 of 7) did so within 6 months of HSCT. The relapsed group demonstrated no statistically significant differences in age, gender, duration of CIDP, MGUS status, baseline nerve conduction studies, or baseline strength examination compared to the drug-free remission group (data not shown).

Minimization of diagnostic errors was accomplished by strict adherence to EFNS/PNS CIDP diagnostic criteria and by exclusion of patients lacking an unequivocal diagnostic evaluation or those with a potential alternative neuropathy etiology. The threshold for re-initiation of immunotherapy after HSCT, i.e. relapse, was low since any patient could have immunotherapy restarted at the discretion of the study team or the independent local neurologist's clinical judgment. In order to avoid selecting patients with long-term inactive disease, patients dependent on conventional therapy with chronic stable deficits required documentation of clinical decline following dose reduction or delay in standard therapy prior to study inclusion. Furthermore, should our results simply been a consequence of getting patients with inactive disease off unneeded immunotherapy we would not have expected interval improvements in strength (MRC sum score), electrophysiology (nerve conduction velocity, conduction block, mean CMAP), and disability (Barthel index, Rankin score, and INCAT scale).

Given the durability of medication free outcome, HSCT may be cost effective compared to maintenance IVIG or plasmapheresis. Non-myeloablative HSCT is a onetime intervention that results in clinically relevant reversal of disability, improvement in CMAP amplitude, NCV, CB, quality of life, and in most cases long- term independence from conventional therapies.

5.3 Summary of HSCT for Multiple Sclerosis and CIDP

HSCT, using non-myeloablative regimens (i.e. not cancer regimens), was performed safely and achieved sustainable prolonged medication free reversal of disability and improvement in quality of life. Unique aspects of each neurological disease impact the outcome of HSCT. For MS, patients need to be selected during the inflammatory stage of disease and fever needs to be avoided by using corticosteroids during HSCT. For CIDP, strict EFNS/PNS criteria need to be used to avoid treating non-CIDP causes of peripheral neuropathy.

6.1 Eligibility Criteria for HSCT of Stiff person Syndrome (SPS)

6.2 Inclusion Criteria (must meet criteria of A or B or C)

A) Diagnosis of Stiff-person Syndrome and

1. Age between 18 and 60 years old
2. Failure of medically tolerable doses (20-40 mg/day) of diazepam
3. Failure of either IVIG and or plasmapheresis
4. Stiffness in the axial muscles, prominently in the abdominal and thoracolumbar paraspinal muscle leading to a fixed deformity (hyperlordosis)
5. Superimposed painful spasms precipitated by unexpected noises, emotional stress, tactile stimuli
6. Confirmation of the continuous motor unit activity in agonist and antagonist muscles by electromyography when off diazepam and anti-spasmotic medications
7. Absence of neurological or cognitive impairments that could explain the stiffness

B) Diagnosis of a SPS variant— Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM) defined as:

1. Acute onset of painful rigidity and muscle spasms in the limbs and trunk
2. Brainstem dysfunction (nystagmus, opsoclonus, ophthalmoparesis, deafness, dysarthria, dysphagia)
3. Profound autonomic disturbance.
4. Positive serology for GAD65 autoantibodies, assessed by immunocytochemistry, western blot or radioimmunoassay (>1000 u/ml)
5. MRI may show increased signal intensity throughout the spinal cord and the brainstem

C) Diagnosis of a SPS variant - anti-GAD positive cerebellar ataxia

1. Subacute or chronic onset of cerebellar symptoms—gait or limb ataxia, dysarthria, nystagmus
2. Positive serology for GAD65 autoantibodies, assessed by immunocytochemistry, western blot or radioimmunoassay (>1000 u/ml)
3. Anti-GAD antibody in cerebrospinal fluid
4. Abnormal MRI imaging of brainstem or cerebellum other than cerebellar atrophy
5. Negative history of toxin or alcohol
6. Absence of Vitamin B12 or Vitamin E deficiency
7. Absence of positive HIV, syphilis or whipple disease
8. Absence of consanguity, positive family history for ataxia or positive genetic screen for SCA1, SCA2, SCA3, SCA6, SCA 7 or SCA8 mutation

6.3 Exclusion criteria for HSCT of Stiff person Syndrome (SPS) and variants

1. Current or prior history of a malignancy or paraneoplastic syndrome
2. Inability to sign and understand consent and be compliant with treatment
3. Positive pregnancy test
4. Inability to or comprehend irreversible sterility as a possible side effect
5. Amphiphysin antibody positive
6. LVEF < 45% or ischemic coronary artery disease on dobutamine stress echocardiogram
7. DLCO < 60% predicted
8. Serum creatinine $\geq$ 2.0 mg/dl
9. Bilirubin >2.0 mg/dl
10. Platelet count < 100,000 / ul, WBC < 1,500 cells/mm^3
11. History of toxin or alcohol abuse
12. History of Vitamin B12 or Vitamin E deficiency
13. Positive HIV, syphilis, or whipple disease
14. Consanguity, positive family history for ataxia or positive genetic screen for SCA1, SCA2, SCA3, SCA6, SCA 7 or SCA8 mutation (if ataxia present)
15. Absence of at least one SPS associated antibody such as anti-GAD, or GABA-A receptor associated protein, or synaptophysin, or gephyrin, or GABA-transaminase
16. Life expectancy less than 1 year

7.0 Study Parameters

Parameter	Pre-HSCT	During hospitalizatio	6 month, 1, 2, 3, 4, 5 years
History and physical	X	daily	X
CBC	X	X	X
Chemistry and creatinine	X	X	X
LFT	X	X (TIW)	X
Dobutamine stress test	X		
EKG	X		
PFT	X		
AntiGAD antibody	X		X
Amphiphysin antibody@	X		X (Only if positive pre HSCT)
EMG	X		X (optional)
Mammogram@	X (optional)		
HRCT@	X		
Abdomen pelvis CT or MRI @	X		
Colonoscopy@	X (optional)		
Anti-Hu@	X		
CEA, CA-125, (PSA -if male)@	X		
HIV, RPR	X		
PCA-1 PCA-2 antibody	X (Only if cerebellar		
MRI brain with gad	X (Only if PERM or cerebellar		
MRI of spine	X		
SCA1,2,3,6,7,8 genes	X (optional)		
Dose diazepam or baclofen	X		X
SF-36	X		X
Timed ambulation	X		X
Chronic Pain Acceptance	X		X
Activities of Daily Living Questionnaire (Barthel	X		X
Rankin Functional Scale	X		X
Modified Ashworth Scale	X (optional)		X (optional)

@ preformed to rule out malignancy

8.1 TREATMENT PLAN

8.2 Mobilization and Peripheral Blood Stem Cell Harvest

The mobilization schedule is outlined in below:

MOBILIZATION AND PBSC HARVEST								
PROCEDURE\DAY	**0**	**1**	**2**	**3**	**4**	**5**	**10+**	**ANC > 1000**
Cyclophosphamide 2.0 gm/m2	X							
G-CSF 5-10 mcg/kg/day SQ						X	X	X*
Prophylaxis Antifungal and Antibiotic (such as fluconazole and amoxicillin/clavulanate)						X		
Apheresis								X*

*Apheresis will begin when the ANC > 1.0 x 10^9/L and continue until >2.0 x 10^6 CD34+ cells/kg patient weight are cryopreserved. A 10-15 liter apheresis will be performed unless stopped earlier for clinical judgment of toxicity (e.g., numbness, tetany). A maximum of four apheresis will be performed. The G-CSF will continue until apheresis is discontinued

8.3 Conditioning regimen

DAY	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**+1**	**+5**
Hydration		X	X	X	X	X			
Cyclophosphamide 50 mg/kg/day		X	X	X	X				
MESNA 50 mg/kg/day		X	X	X	X				
ATG (rabbit)		0.5	1.0	1.0	1.5	1.5			
Methylprednisolone **1 gram**/day		X	X	X	X	X			
Stem cell reinfusion							X		
G-CSF 5 mcg/kg/day									X
Rituxan 500 mg IV (not weight, height adjusted)	X							X	

Cyclophosphamide 50 mg/kg/day will be given IV over 1 hour in 250 cc of normal saline on day –5, -4, -3, and -2. 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 ideal weight. Adjusted ideal weight = ideal weight + 40% x actual weight minus ideal weight.

Mesna 50mg/kg/day will be given IV over 24 hours in 250 cc of normal saline or D5W. Weight base is calculated same as cyclophosphamide as above.

ATG (rabbit) 0.5 mg/kg on day –5; 1mg/kg on day –4 and -3; 1.5 mg/kg on day -2 and -1 (total 5.5mg/kg) will be given IV over 10 hours in 250 cc of normal saline beginning at least 1 hour after infusion of cyclophosphamide. If actual weight is less than ideal weight, rATG will be given based on actual weight. If actual weight is greater than ideal weight, rATG will be given as adjusted weight. Adjusted weight = ideal weight + 25% of [actual weight - ideal weight]. Premedicate with acetaminophen 650 mg po and diphenhydramine 25 mg po/IV 30 minutes before the infusion. An in-line 0.22 µm filter should be used for ATG administration.

Methylprednisolone A suggested dose of 250mg IV should be administered 30 minutes before each ATG infusion.

Hydration A suggested rate of 125 cc/hr NS should be given starting 6 hours before cyclophosphamide and continue until 24 hours after the last cyclophosphamide dose. The rate of hydration will be aggressively adjusted in order to avoid fluid overload. BID weights will be obtained. Amount of fluid can be modified based on patient's fluid status. Minimum target urine output is 2 liters/m^2/day

G-CSF 5 mcg/kg/day SQ will be continued until the absolute neutrophil counts reach at least 500/µl.

Rituxan 500 mg will be given IV on the day before the first dose of ATG and the day after stem cell infusion.

9.0 SUPPORTIVE CARE GUIDELINES (may vary according to institutional guidelines)

9.1 Infection Prophylaxis Guidelines -These are guidelines for autoimmune disease (not cancer) and are consistent with all our FDA approved phase I, II, and III (randomized) studies for HSCT of autoimmune diseases

All prophylactic antibiotics may be changed or discontinued according to clinical circumstances (such as patient's allergy) as determined by attending physician(s).

9.11 Bacterial infection prophylaxis. When WBC/ANC drops, or on day 0, a broad spectrum intravenous antibiotic such as piperacillin/tazobactam or cefepime (pseudomonal coverage is needed) will be initiated regardless of temperature until the ANC returns to > 500/µl. If fever occurs or patient has a history of surgical hardware or other risk for infection, antibiotic coverage will be expanded to include vancomycin (unless allergy). Patients with a history of allergy to penicillin or cephalosporin must be evaluated by an allergist for

testing prior to stem cell transplant. Once the WBC engraft and patient is without sign of infection and/or fever, intravenous antibiotics will be stopped. Administration of antibiotics will be done according to the institutional standard of practice of the participating center.

9.12 Pneumocystis prophylaxis. Upon admission, pentamidine nebulizer 300mg will be given. Bactrim DS one tablet q.a.m on Monday, Wednesday, and Friday will be started after complete engraftment and will be continued as long as patient is on immunosuppressive medicine or 6 months, whichever comes later. If patient has sulfa allergy or poor engraftment, aerosolized pentamidine inhalation 300 mg/month will be performed for same duration.

9.13 Antifungal prophylaxis. Isavuconazole 372 mg by mouth daily will start on day +2 and continued until discharge from hospital. At discharge, antifungal will be switched to fluconazole 400 mg PO daily for six months post-transplant. Other antifungals such as voriconazole or posaconazole may be used. Antifungal medications may be held, discontinued, or switched for adverse side effects, for elevated transaminases, or to change coverage of fungal organism depending on clinical situation.

9.14 Antiviral prophylaxis. Valtrex 500 mg po BID (or equivalent antiviral drugs that have activity to HSV & VZV with equivalent dosage) will be started on day admission and continued for 12 months.

9.15 Signs of infection. If patient has signs of infection, choice and duration of antibiotics will be decided by attending physician's discretion. Dosage adjustment is required if patient has organ dysfunction.

9.2 Transfusion Guidelines

All blood products need to be leukoreduced, irradiated and, preferably, CMV compatible.

9.21 Platelet counts. Will be kept 10,000 or more throughout transplant period.

9.22 RBC counts. Threshold to RBC transfusion will be determined by patient's condition; in general, hemoglobin level >8.0 is preferable.

9.3 Other Supportive Care Guidelines

9.31 Respiratory care. Incentive spirometry will be performed several times/day to prevent atelectasis.

9.32 Nutrition. If patient cannot take oral intake, TPN is recommended during the peri-transplant period. During neutropenia, a low bacterial diet will be provided.

10.1 HOSPITAL DISCHARGE GUIDELINES

1. Afebrile.
2. Platelet transfusion independent.
3. Neutrophil count greater than 500/ul.

11.0 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 and ATG and rituximab and methylprednisolone will suppress the hematopoietic ability of the patient's marrow, and leave the patient susceptible to a wide variety of infections and bleeding complications until the re-infused marrow engrafts.

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, prior exposure to prolonged or aggressive chemotherapy regimens, conditioning regimen, source of stem cells and type of graft. Transplant related complications include infections, bleeding, veno-occlusive disease of the liver, and failure to engraft. This protocol is designed to minimize all these complications.

Risk of PICC line and apheresis catheter. 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 PBSC collection. This procedure requires 4-6 hours and will be performed through an 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 12 - Drug Information.

12.0 DRUG INFORMATION

12.1 ATG (rabbit)

12.11 Other names: thymoglobulin.
12.12 Description: A rabbit polyclonal antibody to lymphocytes.
12.13 Drug administration: Diluted in 250 NS and infused over 10 hours.
12.13 Storage and Stability: 50mg/ml (5 ml ample) vial stored in refrigerator.
12.14 Toxicity: Side effects of ATG are serum sickness and/or anaphylaxis: chills, arthralgias, headache, myalgias, nausea, vomiting, diarrhea, chest-pain, hypotension, dyspnea, pulmonary edema, abdominal pain. Other side effects include abnormal liver function tests (SGOT,

SGPT) abnormal renal function, and thrombocytopenia.

12.2 Cyclophosphamide

12.21 Other names: Cytoxan, Neosar
12.22 Chemical: 2-bis (2-chloroethyl) amino tetrahydro-2H-1, 3, 2- oxazaphosphorine-2-oxide monohydrate.
12.23 Classification: Alkylating agent.
12.24 Action: Causes prevention of cell division by forming adducts with DNA.
12.25 Metabolism: Metabolized to active compounds by microsomal enzymes in the liver. Excreted by the kidney in both the original form and as metabolites.
12.26 Availability: 25 mg and 50 mg tablets (tablets cannot be split); 100 mg, 200 mg, 500mg, 2000 mg vials Mead Johnson and Adria.
12.27 Storage: Stable at room temperature indefinitely before reconstitution. After reconstitution, stable for 6 days upon refrigeration or for 24 hours at room temperature.
12.28 Administration: Dissolved in 250 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.
12.29 Side effects: Myelosuppression, leukopenia (nadir 8-14 days), hemorrhagic cystitis, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), bladder carcinoma, cellular dysplasia, 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.

12.3 G-CSF

12.31 Other name: Neupogen.
12.32 Description: hematopoietic growth factor.
12.33 Drug administration: subcutaneous administration 5-15 mcg/kg/day.
12.34 Storage and Stability: 300 mcg and 480 mcg vials stored in refrigerator.
12.35 Toxicity: myalgias, headache, flu-like symptoms, fever, bone pain in approximately 20% of patients, possible elevation of uric acid, transaminases, and LDH.

12.4 Mesna

12.40 Other name: Mesnex
12.41 Description: detoxifying agent inhibit the hemorrhagic cystitis

induced by cyclophosphamide.

12.42 Drug administration: intravenous infusion over 24-hour period. Dosagewill be equivalent to 60-100% of total cyclophosphamide dosage.

12.43 Storage and Stability: Stored at room temperature 15-30°C. Dilute with D5W or normal saline at final concentration of 20mg/ml. The diluted solution is chemically and physiologically stable 24 hours at 25°C

12.44 Toxicity: bad taste in the mouth, soft stool, headache, fatigue, nausea, diarrhea, limb pain, hypotension and allergy.

12.5 Rituximab

12.50 Other name: rituxan

12.51 12.51 Description: is a chimeric monoclonal antibody used in the treatment of B cell non-Hodgkin's lymphoma, B cell leukemia, and some autoimmune disorders.

12.52 Drug administration: The recommended dosage for patients with low grade or follicular NHL is 375 mg/m2 infused intravenously. In autoimmune diseases the standard dosing for adults is usually 500 mg not adjusted for weight or height. The infusion is given at weekly intervals for four total dosages. Acetaminophen and diphenhydramine hydrochloride are given 30-60 minutes before the infusion to help reduce side effects. If given as a retreatment the dosage is the same. Clinical trials were ongoing in 2001 to help clarify the ideal dosage and treatment schedule for this drug. Generally, decrease in symptoms occurs at an average of 55 days after the last administration of the antibody.

12.53 Side effects: The majority of side effects occur after or during the first infusion of the drug. Some common side effects include dizziness, feeling of swelling of tongue or throat, fever and chills, flushing of face, headache, itching, nausea and vomiting, runny nose, shortness of breath, skin rash, and unusual fatigue.

13.0 EVALUATION OF TOXICITY (Daily while hospitalized and on return evaluations)

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

14.1 ADVERSE EVENT REPORTING

Any serious unexpected event **or** any death within 30 days of study treatment must be immediately reported, regardless of the cause, to Richard Burt MD (312-695-4960).

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

a) All life-threatening and lethal (Grade 4 and 5) unanticipated reactions. Grade 4 myelosuppression is an anticipated reaction of HSCT. The spectrum of SPS includes insulin dependent diabetes often with poorly controlled blood sugars and spasms of abdominal pain. In patients with SPS, light touch such as a blood pressure cuff or noise such as conversation can precipitate skeletal or abdominal spasms with pain, nausea, and diarrhea. Therefore, transient Grade 4 hyperglycemia is an anticipated reaction in patients with a comorbidity of diabetes. Grade 4 vomiting and anorexia are also anticipated reactions.

14.2 To be reported in writing within 10 working days:

a) Life-threatening and lethal (Grade 4 and 5) unexpected reactions (Grade 4 myelosuppression is expected with HSCT). Grade 4 hyperglycemia is expected in SPS patients with SPS-related diabetes. In patients with SPS, light touch such as a blood pressure cuff or noise such as conversation can precipitate skeletal or abdominal spasms with pain, nausea, and diarrhea. Grade 4 vomiting and anorexia is expected due to complications of SPS causing spasms of abdominal pain.)
b) Any death within 30 days of study treatment.

15.0 EVALUATION OF RESPONSE - To be performed at 6 and 12 months post- transplant, and annually thereafter for 5 years.

1 Primary end point – Overall Survival
2. Disease improvement **--** Disease improvement
- Decrease (50%) and complete discontinuation of muscle relaxation anti- spasmotic medications
- Chronic Pain acceptance questionnaire (CPAQ) (appendix I)
- Timed ambulation
- Activities of Daily Living (appendix II)
- SF-36 QOL (Appendix III)
- Rankin Functional Scale (appendix IV) (Improvement for disability scales is defined in the same manner as for the SF-36 QOL, that is whether or not there is a statistically significant change in the score / scale / dimension done by standard statistical methodology such as student t test or mixed method analysis.

16.1 BIOSTATISTICAL CONSIDERATIONS

This is a phase I/II study of 40 patients. Statistical considerations and safety rules for the protocol are as follows:

16.2 Stopping rules for transplant-related regimen-related toxicity. Regimen- related toxicity within the first 28 days after transplant will be determined as follows: non-hematological grade 4 toxicity that fails to

resolve in 10 days; and hematological grade 4 toxicity that fails to resolve in 28 days. Operationally sufficient evidence of any ratio of regimen-related toxicity will occur when any of the following ratios is observed: any 2/10, 4/20, 8/40.

16.3 Stopping rules for transplant-related mortality (TRM). TRM will be defined as death within the first 100 days of transplant due to transplant-related complications. Operationally, this will occur with any 2 of 10 deaths.

16.4 Any death within the first 100 days will result in halting the study until reviewed and the IRB and FDA notified.

17.1 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.

18.0 REGISTRATION PROCEDURE

Patients must not start protocol treatment prior to registration. When eligibility is confirmed by the physician and nurse, and the protocol checklist is initialed and signed by the physician and nurse, the patient will be entered.

19.1 RECORDS TO BE KEPT

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

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APPENDIX I

Chronic Pain Acceptance Questionnaire (CPAQ)

Below you will find a list of statements. Please rate the truth of each statement as it applies to you.

Use the following rating scale to make your choices. For instance, if you believe a statement is 'Always True,' you would write a 6 in the blank next to that statement

0	1	2	3	4	5	6
Never True	**Very Rarely True**	**Seldom True**	**Sometimes True**	**Often True**	**Almost Always True**	**Always True**

1. I am getting on with the business of living no matter what my level of pain is _____

2. My life is going well, even though I have chronic pain _____

3. It's OK to experience pain _____

4. I would gladly sacrifice important things in my life to control this pain better _____

5. It's not necessary for me to control my pain in order to handle my life well _____

6. Although things have changed, I am living a normal life despite my chronic pain _____

7. I need to concentrate on getting rid of my pain _____

8. There are many activities I do when I feel pain _____

9. I lead a full life even though I have chronic pain_____

10. Controlling pain is less important than any other goals in my life _____

11. My thoughts and feelings about pain must change before I can take important steps in my life _____

12. Despite the pain, I am now sticking to a certain course in my life _____

13. Keeping my pain level under control takes first priority whenever I'm doing something _____

14. Before I can make any serious plans, I have to get some control over my pain _____

15. When my pain increases, I can still take care of my responsibilities _____

16. I will have better control over my life if I can control my negative thoughts about pain _____

17. I avoid putting myself in situations where my pain might increase _____

18. My worries and fears about what pain will do to me are true _____

19. It's a relief to realize that I don't have to change my pain to get on with my life _____

20. I have to struggle to do things when I have pain _____

REFERENCE- *McCracken LM, Vowles KE, Eccleston C, Pain 107, 2004, 159-166*

APPENDIX II

Activities of Daily Living (Barthel Index)

THE BARTHEL INDEX

Patient Name: _____
Rater Name: _____
Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

APPENDIX III

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)

Excellent 1

Very Good 2

Good 3

Fair 4

Poor 5

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

Much better now than one year ago 1

Somewhat better now than one year ago 2

About the same as one year ago 3

Somewhat worse now than one year ago 4

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, Not A Little	No 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

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

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

Circle one

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
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 Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
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 --

	All of the Time	Most Bit of Time	A Good of the Time	Some of the Time	A Little of the Time	None the of 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 All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

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

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
	(circle one number on each line)				
a. I seem to get sick a little easier than other people.	1	2	3	4	5
b. I am healthy as anybody I know.	1	2	3	4	5
c. I expect my health to get worse.	1	2	3	4	5
d. 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 IV

Rankin Functional Score

0: **Asymptomatic**

1: **Nondisabling symptoms that do not interfere with life-style.**

2: **Minor disability symptoms that lead to some restriction of life-style but do not interfere with the patients' capacity to look after themselves.**

3: **Moderate disability symptoms that significantly interfere with life-style or prevent totally independent existence.**

4: **Moderately severe disability symptoms that clearly prevent independent existence, although patient does not need constant attention day and night.**

5: **Severely disabled, totally dependent requiring constant attention day and night.**

Patient Name_____ **Date**_____

APPENDIX V

Modified Ashworth Scale

The Modified Ashworth Scale (MAS) measures resistance during passive soft-tissue stretching. It is a quick and easy measure that can help assess the efficacy of treatment. The following conventions prevail:

- The MAS is performed in the supine position (this will garner the most accurate and the lowest score as any tension anywhere in the body will increase spasticity)
- Because spasticity is "velocity dependent" (the faster the limb is moved, the more spasticity is encountered), The MAS is performed while moving the limb at the "speed of gravity"' this is defined as the same speed at which a non-spastic limb would naturally drop (fairly fast)
- The test is performed a maximum of three times for each joint; if more than three times, the short-term effect of a stretch can influence the score
- The MAS is performed prior to goniometric testing; goniometric testing provides a stretch, and the short-term effect of a stretch can influence the score

Scoring

0 = Normal tone, no increase in tone
1 = Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the range of motion (ROM) when the affected part(s) is moved in flexion or extension
1+= Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2 = More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved 3 = Considerable increase in muscle tone, passive movement difficult
4 = Affected part(s) rigid in flexion or extension

Positions

The positions used for an MAS assessment are as follows:

Score_____Elbow. *Start position:* Elbow fully flexed, forearm neutral. Movement: Extend elbow from maximum possible flexion to maximum possible extension. (Triceps would be in the same position, opposite direction.)

Score_____Wrist. *Start position:* Elbow as straight as possible, forearm pronated. Movement: Extend the patient's wrist from maximum possible flexion to maximum possible extension.

Score_____Fingers. *Start position:* Elbow as straight as possible, forearm neutral. All fingers are done at once. Movement: Extend the patient's fingers from maximum possible flexion to maximum possible extension.

Score_____Thumb. *Start position:* Elbow as straight as possible, forearm neutral, wrist neutral. Movement: Extend the thumb from maximum possible flexion (thumb against index finger) to maximum possible extension (in anatomical position, "abducted").

Score_____Hamstrings. *Start position:* Prone so that ankle falls beyond end of the plinth, hip in neutral rotation. Movement: Extend the patient's knee from maximum possible flexion to maximum possible extension

Score_____Quadriceps. *Start position:* Prone so that ankle falls beyond end of the plinth, hip in neutral rotation. Movement: Flex the patient's limb from maximum possible flexion to maximum possible extension

Score_____Gastrocnemius. *Start position:* Supine, ankle plantarflexed, hip in neutral rotation and flexion. Movement: Dorsiflex the patient's ankle from maximum possible plantarflexion to maximum possible dorsiflexion not more than three consecutive times and rate the muscle tone.

Score_____Soleus. *Start position:* Supine, ankle plantarflexed, hip in neutral rotation and flexion and with the knee flexed to -15$_0$. Movement: Dorsiflex the patient's ankle from maximum possible plantarflexion to maximum possible dorsiflexion