ORIGINAL CONTRIBUTION

High-Dose Cyclophosphamide for Moderate to Severe Refractory Multiple Sclerosis

Douglas E. Gladstone, MD; Kenneth W. Zamkoff, MD; Lauren Krupp, MD; Robert Peyster, MD; Patrick Sibony, MD; Christopher Christodoulou, PhD; Emily Locher, RN; Patricia K. Coyle, MD

Background: High-dose cyclophosphamide is active in immune-mediated illnesses.

Objective: To describe the effects of high-dose cyclophosphamide on severe refractory multiple sclerosis.

Design, Setting, and Patients: Patients with multiple sclerosis with an Expanded Disability Status Scale (EDSS) score of 3.5 or higher after 2 or more Food and Drug Administration–approved disease-modifying therapy regimens were evaluated.

Interventions: Patients received 200 mg/kg of cyclophosphamide over 4 days.

Main Outcome Measures: Patients had brain magnetic resonance imaging and neuro-ophthalmologic evaluations every 6 months and quarterly EDSS and quality-of-life evaluations for 2 years.

Results: Twelve patients were evaluated for clinical response (median follow-up, 15.0 months; follow-up range, 6-24 months). During follow-up, no patients increased their baseline EDSS scores by more than 1.0. Five patients decreased their EDSS scores by 1.0 or more (EDSS score decrease range, 1.0-5.0). No patient had a new lesion on brain magnetic resonance imaging. No patient showed any enhancing lesions. Patients reported improvement in all of the quality-of-life parameters measured. Neurologic improvement involved changes in gait, bladder control, and visual function. Treatment response was seen regardless of the baseline presence or absence of contrast lesion activity. Patient quality-of-life improvement occurred independently of EDSS score changes. In this small group of patients with treatment-refractory multiple sclerosis, high-dose cyclophosphamide was associated with minimal morbidity and improved clinical outcomes.

Conclusions: High-dose cyclophosphamide treatment in patients with severe refractory multiple sclerosis can result in disease stabilization, improved functionality, and improved quality of life. Further studies are necessary to determine the most appropriate patients for this treatment.

Arch Neurol. 2006;63:(doi:10.1001/archneur.63.10.noc60076)

MULTIPLE SCLEROSIS (MS) is a major disabling neurologic disease of young adults[1] and represents the most common immune-mediated inflammatory and demyelinating disorder of the central nervous system.[2] The disability that MS produces is underscored by nearly 50% of patients who will require ambulatory aids within 15 years after disease onset.[3] Currently, there is no cure for MS. Therapy is targeted at changing the short-term natural history of MS to decrease relapse rates and to postpone long-term disability.[4]

High-dose cyclophosphamide (HDC) is a chemotherapy treatment option for severe, refractory, immune-mediated illnesses. The goal of HDC is to eradicate B and T cells responsible for disease while sparing the pluripotent blood stem cells from any ill effect. Since 1996, multiple articles[5-9] on numerous immune-mediated illnesses have shown that HDC decreases disease activity and improves quality of life (QOL).

Here we describe our experience with HDC (investigational new drug No. 65863) for severe refractory MS. The treatment goal was to stop disease progression rather than to induce disease regression (ie, resolution of fixed neurologic deficits).

METHODS

All of the patients signed an informed consent form approved by the internal review board of Stony Brook University, Stony Brook, NY. Thirteen patients met the diagnosis of MS as outlined by the McDonald International Panel Diagnostic Criteria.[10] All of the patients had an Expanded Disability Status Scale (EDSS) score of 3.5 or higher. They all had active disease despite a minimum of 2 Food and Drug Administration–approved disease-modifying therapies. For patients with relapsing-remitting

Author Affiliations: Departments of Medicine (Drs Gladstone and Zamkoff and Ms Locher), Neurology (Drs Krupp, Christodoulou, and Coyle), Radiology (Dr Peyster), and Ophthalmology (Dr Sibony), State University of New York at Stony Brook.

Table 1. Patient Characteristics

Patient No./ Sex/Age, y	MS Subtype	Disease Duration, y	Baseline EDSS Score	Previous Treatment							
				Steroids	IM INF-β1a, y	SC INF-β1b, y	SC IFN-β1a, y	Glatiramer Acetate, y	IVIg	Mitoxantrone Hydrochloride, mg/mm	Other
1/F/45	RR	15.4	5.0	+	–	0.7	0.75	2.00	–	–	T-cell receptor peptide study
2/M/40	RR	17.7	4.0	+	1.5	2.3	–	0.25	+	92	–
3/F/48	SP	5.8	8.0	+	5.5*	–	–	–	–	65	–
4/F/46	SP	17.1	6.5	+	–	1.0	–	6.20*	–	72	Azathioprine, 1.5 y; MTX, 18 g/wk for 10 mo
5/F/40	SP	22.0	6.5	+	–	7.2*	–	–	–	–	–
6/F/41	SP	13.0	6.5	+	0.4*	8.4	–	–	+	48	–
7/F/51	SP	19.2	7.0	+	–	1.0	–	–	–	54	Cyclophosphamide, 1 g/mo for 2 y
8/F/26	RR	3.1	5.5	+	2.0	–	0.50*	–	–	–	–
9/F/28	RR	6.5	5.5	+	5.2	1.0*	–	–	–	36	–
10/F/42	SP	29.0	7.5	+	–	11.5*	0.25	–	–	–	–
11/F/27	RR	5.8	6.0	+	–	5.5*	–	–	–	–	–
12/F/52	SP	16.0	4.5	+	–	4.0	2.25*	–	–	–	–
13/F/20	RR	8.5	6.5	+	0.6*	7.2	–	0.83	+	75	Natalizumab, plasmapheresis, and pulse cyclophosphamide, 750 mg/mm × 5 over 8 mo

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; INF, interferon; IVIg, intravenous immunoglobulin; MS, multiple sclerosis; MTX, methotrexate; RR, relapsing-remitting; SC, subcutaneous; SP, secondary progressive; +, treatment received; –, treatment not received.
*Therapy was stopped less than 3 months before high-dose cyclophosphamide treatment.

disease, treatment failure was defined as 2 or more relapses during the prior year. For patients with secondary progressive disease, treatment failure was defined as objective deterioration on neurologic examination during the prior year. All of the remittive therapies except for steroids were stopped 3 weeks before the HDC treatment; given such active disease, a washout period was not ethical. All of the patients had preserved cardiac and renal function.

Patients received 200 mg/kg of cyclophosphamide based on adjusted ideal body weight over 4 days. Hemorrhagic cystitis prophylaxis consisted of mesna and forced diuresis. Patients received antibacterial, antiviral, and antifungal prophylaxis. Irradiated blood-product transfusions maintained a hemoglobin concentration greater than 8.5 g/dL and a platelet count greater than 10×10^9/L. Patients with febrile neutropenia received broad-spectrum antimicrobials. Starting on day 10, patients received 5 µg/kg of filgrastim per day until their absolute neutrophil count rose to 1.0×10^9/L for 2 consecutive days.

Baseline evaluation included EDSS score, brain magnetic resonance imaging (MRI) with and without contrast, and neuroophthalmic assessment. Patients had repeat MRI and neuroophthalmic assessments every 6 months and quarterly EDSS evaluations for 2 years. A sustained EDSS response was defined as a decrease of 1.0 or more on 2 sequential evaluations. Sustained EDSS score worsening was defined as an increase of 1.0 or more on 2 sequential evaluations. On brain MRI, the number of T2-weighted and enhancing lesions was classified into the following groups: 1 to 5, 6 to 10, 11 to 15, and more than 15 lesions.

Quality of life in 10 patients was measured by Short Form 36.[11] Data were analyzed using SF Health Outcomes Scoring Software (QualityMetric, Inc, Lincoln, RI) to create norm-based scoring using means and SDs from the 1998 US general population. The norm-based scores in the US general population have a mean of 50 and an SD of 10. Additional summary physical composite and mental composite scores were derived. Changes in fatigue were assessed in 8 patients using the Fatigue Severity Scale (FSS), a self-administered questionnaire. In this scale, scores range from 1 to 7; scores of 4 or higher represent significant clinical fatigue.[12]

RESULTS

PRETREATMENT EVALUATION

Patient characteristics and treatment histories are summarized in **Table 1**. The 13 patients had a median age of 41.0 years (range, 26-52 years), a median EDSS score of 6.5 (range, 4-8), and a median disease duration of 15.4 years (range, 3.1-29.0 years). Seven (54%) of the 13 patients had secondary progressive disease. Seven (54%) had previously received mitoxantrone hydrochloride. Eleven (85%) received therapy within 90 days of the first dose of cyclophosphamide. All of the patients had deterioration of their neurologic examination results during a 12-month period before the first HDC evaluation despite at least 2 standard MS disease-modifying therapies (**Table 2**).

IMMEDIATE CHEMOTHERAPY EFFECTS

Patients experienced absolute neutropenia for a median of 9 days (range, 6-12 days), received a median of 1.0 unit (range, 0-3 units) of packed red blood cells, and received a median of 1.0 single-unit donor platelet infu-

sion (range, 0-3 single-unit donor platelet infusions). Patients tolerated the treatment well. Only expected toxicities were observed: 6 (46%) had febrile neutropenia, nausea controlled with antiemetics was common, and serum chemistry abnormalities were transient and corrected with fluids and electrolyte administration. No patient experienced long-term morbidity or required rehospitalization after discharge.

NEUROLOGIC ASSESSMENT

The median follow-up for the 12 clinically evaluated patients was 15.0 months (range, 6-24 months). The EDSS responses are shown in **Table 3**. Five patients (42%) met the study criteria for a sustained response, with a decrease of 1.0 or more in their EDSS scores (range of decrease, 1.0-5.0). No patient showed sustained worsening (EDSS increase >1.0).

All of the patients had bladder problems before HDC treatment. Nine (75%) of 12 patients reported improved bladder function after treatment. Before HDC treatment, patient 2 had marked urgency, weekly incontinence, and required oxybutynin chloride and intranasal desmopressin acetate. After treatment, his bowel and bladder function score remains at 2, but he stopped receiving all of the medications and has incontinence twice per month. Eight patients had decreased bowel and bladder function scores, and 6 (50%) experienced complete symptom resolution.

After 14 months, patient 4 withdrew from the study. Her EDSS score was stable throughout the observation period. Patient 6 showed an EDSS score decrease of 0.5 at 6 months. At 8.4 months after therapy, during active bronchitis, her EDSS score returned to 6.5 and she received a 3-day course of intravenous methylprednisolone without effect. She has received no further therapy and has not experienced further worsening. During a herpes zoster oticus infection 407 days after therapy, patient 5 had an abrupt return of her spasticity, reversing a reduction of 1.5 in her EDSS score. Treated with pulse steroids and currently on a steroid taper, her baseline gait has returned. No other patient is receiving any other form of remittive therapy.

Table 2. Disease Activity in the Year Before High-Dose Cyclophosphamide Treatment

Patient No.	Disease Subtype	Disease Activity in the Year Before HDC Treatment
1	RR	2 Relapses
2	RR	Worsening on cognitive function testing
3	SP	Worsening motor deficits
4	SP	Worsening motor deficits, new brain MRI lesions
5	SP	Worsening gait deficits
6	SP	Worsening gait deficits
7	SP	Worsening motor and brainstem deficits
8	RR	3 Relapses, worsening bladder function
9	RR	1 Relapse, worsening motor and cerebellar deficits
10	SP	Worsening motor deficits
11	RR	2 Relapses
12	SP	Worsening motor and cerebellar deficits, new brain MRI lesions
13	RR	3 Relapses, new brain MRI lesions, worsening cerebellar deficits

Abbreviations: HDC, high-dose cyclophosphamide; MRI, magnetic resonance imaging; RR, relapsing-remitting multiple sclerosis; SP, secondary progressive multiple sclerosis.

RADIOGRAPHIC ASSESSMENT

The MRI results are provided in **Table 4**. All of the patients had abnormal baseline brain MRI results consistent with MS.[13] Eleven patients had imaging studies at a central location, allowing for more precise evaluations. Nine (82%) of 11 patients had 15 or more lesions. During the follow-up period, no patient had a significant change in the number of lesions. At 2 years, patient 2 had 1 new nonenhancing medullary lesion. Two (18%) of 11 patients had a single enhancing lesion at baseline; these lesions resolved after HDC treatment. At 12 months, patient 5 showed 1 new enhancing lesion without a corresponding high-intensity T2-weighted or fluid-attenuated inversion recovery signal.

Table 3. Expanded Disability Severity Scale Scores Initially vs at Last Follow-up

		Expanded Disability Severity Scale Score															
		Pyramidal		Cerebellar		Brain Stem		Sensory		Bowel and Bladder		Optic		Cerebral		Overall Score	
Patient No.	Follow-up, mo	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
1	24	1	3	1	2	0	2	1	3	6	3	2	3	0	1	5.0	4.0
2	24	3	3	2	2	2	2	2	4	2	2	1	0	2	0	4.0	4.0
3	18	3	5	2	0	2	0	2	3	2	3	3	2	1	0	8.0	8.0
4	9	3	4	1	1	0	0	1	2	1	3	1	1	0	0	6.5	6.5
5	18	3	4	3	2	0	0	3	3	3	0	2	1	0	0	6.5	6.5
6	18	3	3	0	0	0	0	3	3	2	0	2	2	0	0	6.5	6.5
7	15	3	2	2	2	3	4	3	1	2	0	3	1	0	0	7.0	6.5
8	15	2	1	1	0	0	0	3	2	1	0	0	0	0	0	5.5	2.0
9	12	3	3	3	3	1	0	3	2	2	0	2	1	0	0	5.5	4.0
10	6	3	4	0	1	1	1	2	3	4	5	3	2	0	0	7.5	8.0
11	6	3	0	2	0	3	0	2	1	3	0	0	0	0	0	6.0	1.0
12	6	3	1	3	1	3	0	3	3	2	1	1	0	0	0	4.5	3.0

Table 4. Magnetic Resonance Imaging Results Before Therapy vs at Last Follow-up

Patient No.	Follow-up, mo	Lesions, No.		Enhancing Lesions, No.		Comments
		Pretherapy	Posttherapy	Pretherapy	Posttherapy	
1	24	>15	>15	1	0	At 6 mo, 2 lesions became significantly smaller
2	24	>15	>15	0	0	At 24 mo, 1 new medullary lesion
3	18	>15	>15	0	0	NA
4	12	>15	>15	0	0	NA
5	12	>15	>15	0	0	No corresponding T2-weighted or FLAIR lesions at new enhancing site
6	18	>15	>15	0	1	NA
7	12	11-15	11-15	0	0	NA
8	12	>15	>15	1	0	Previous enhancing lesion is smaller and no longer enhances
9	12	NA	NA	NA	NA	Scans not internally reviewed
10	6	>15	>15	0	0	NA
11	6	6-10	6-10	0	0	NA
12	6	>15	>15	0	0	NA

Abbreviations: FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

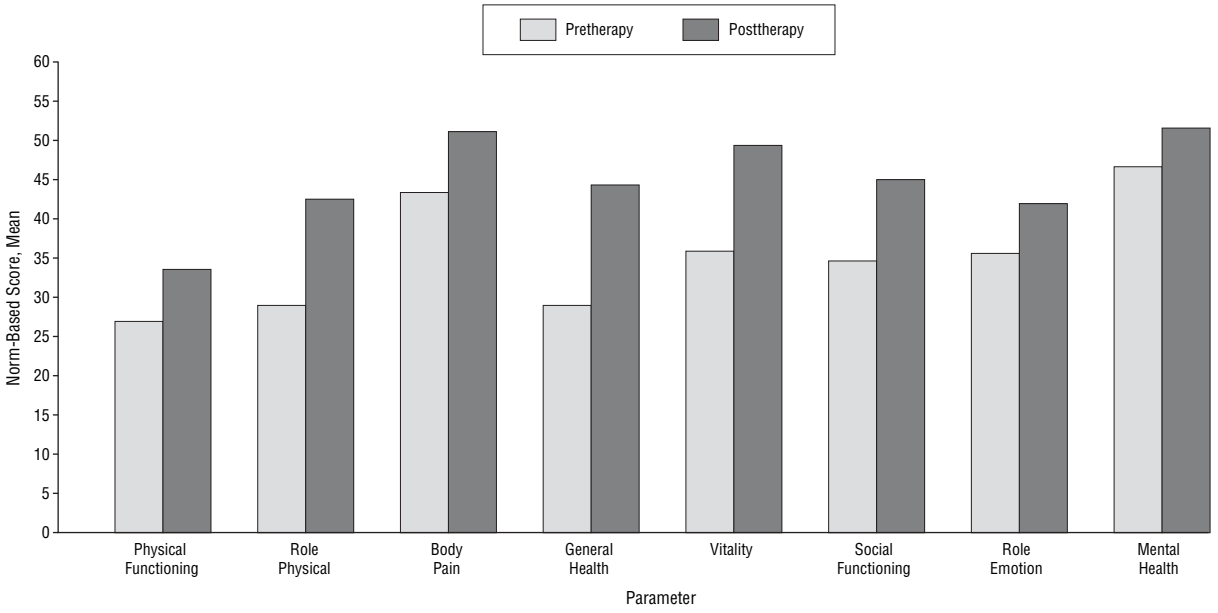

Figure. Pretherapy vs posttherapy average Short Form 36 sum scores.

NEURO-OPHTHALMIC ASSESSMENT

Baseline visual acuity in 2 patients was normal and remained stable. Visual acuity in 4 (44%) of 9 patients improved by 2 or more lines on Snellen eye chart examination; this included patient 7, whose visual acuity changed from 20/60 OD and 20/50 OS to 20/20 OU. Color perception improved in 5 patients as measured by American Optical Hardy-Rand-Rittler pseudoisochromatic plates. It improved by 1.5 plates in patients 4, 9, and 12, by more than 2 plates in patient 10, and by more than 3 plates in patient 1.

QOL ASSESSMENT

The patients reported a major improvement in QOL. Pre–Short Form 36 and post–Short Form 36 summary measure scores (by norm-based scoring) are provided (**Figure**). Before therapy, patients reported a poor QOL as compared with US norms in all of the measured parameters, with a mean physical composite score of 28.3 (score range, 11.6-39.5) and a mean mental composite score of 43.4 (score range, 26.1-57.7). The 1-year evaluation for 7 patients with a follow-up of 1 year or longer (data not shown) showed that their mean physical composite score rose to 38.0 (increase of 9.7; score range, 27.8-54.8), and their mean mental composite score rose to 51.9 (increase of 8.5; score range, 34.9-63.9).

At last follow-up, improvement occurred for all of the 10 patients in each of the 8 measured components. Moreover, an increase of 10 or more points (or a 1-SD increase) occurred in 4 (50%) of 8 measured Short Form

36 scales, including role physical, general health, vitality, and social functioning. The groups' mean physical composite score rose to 40.2 (increase of 11.9; score range, 27.8-65.4), and their mean mental composite score rose to 50.2 (increase of 6.8; score range, 28.6-64.8).

Seven (88%) of 8 patients reported a fatigue reduction. Before therapy, the groups' median FSS score was 6.3 (score range, 1.7-7.0). At last follow-up, the groups' median FSS score was 4.3 (decrease of 2.0; score range, 2.8-7.0). Five patients experienced an FSS score reduction of 1 or more.

COMMENT

The rationale for using HDC in MS is based on treating other refractory immune-mediated neurologic diseases.[6,7] Cyclophosphamide, dosed at 200 mg/kg, eradicates lymphocytes but allows for spontaneous hematopoietic recovery. Thus, lymphocyte immune-mediated illnesses should be responsive to HDC.

This study demonstrated that HDC is well tolerated and that patients with MS do not experience a unique toxicity profile.[6-8] All of the patients experienced full and spontaneous hematopoietic recovery.

All of the patients in this trial had moderate to severe MS with a median EDSS score of 6.5. Seven patients had secondary progressive disease, an MS subtype less responsive to therapies.[3] After HDC treatment, no patient met study criteria for disease progression. Further, 5 (42%) of the patients showed a decrease of 1 or greater in their EDSS scores. Subset analysis of the EDSS score changes revealed improvement in 3 general areas: for ambulation (the major determinant of the EDSS score), 3 patients improved to full ambulatory status, walking without an aid or rest for 500 m; for urinary function, 5 patients (including 2 patients with previous incontinence) experienced full resolution of urinary symptoms; and for visual function, patients' performance improved in separately measured parameters of visual acuity and color perception.

Baseline radiographic imaging revealed a high number of lesions consistent with this cohort's disease severity. Clinical improvement was not limited to those with baseline enhancing lesions. This finding differs from the current hematopoietic stem cell transplantation (HSCT) trial in Europe.[14] During follow-up, only 1 patient developed 1 new enhancing lesion that was not associated with a T2-enhanced or fluid-attenuated inversion recovery signal.

Currently, the only Food and Drug Administration–approved chemotherapy for MS is mitoxantrone. Neutropenia 10 days after infusion is common. During this time, patients with MS are at increased risk for urinary infections and pneumonia. There is a 14% incidence of permanent amenorrhea for women older than 35 years. Clinically significant heart failure is rare, with an estimated prevalence of 0.15%. At 30 months' follow-up, asymptomatic cardiac dysfunction is more common at 2% and rises to 5% when doses of mitoxantrone hydrochloride exceed 100 mg/mm. However, patients with adverse cardiac history, prior radiation, or chemotherapy use may experience heart dysfunction earlier. Mitoxantrone rarely causes acute myeloid leukemia. These leukemias often develop within 2 years of treatment.[15]

Comparatively, HDC requires central access, and nausea and vomiting are common. The incidence of hemorrhagic cystitis is 2%. The incidence of a transient dilated cardiomyopathy is 1%. High-dose cyclophosphamide always results in neutropenia. Overall, the incidence of mortality secondary to HDC is approximately 1%. These risks are comparable to those encountered with HSCT.

However, HDC is strikingly different from HSCT. First, stem cell mobilization is unnecessary, avoiding MS exacerbations associated with filgrastim[16] and removing the risk of autoreactive lymphocyte reinfusion, likely the cause of the disappointing results seen with HSCT.[17,18] Second, posttransplantation antilymphocyte therapy, shown to increase the procedure's mortality and morbidity, is unnecessary.[19,20] Saccardi et al[21] described such an approach. Stem cell mobilization required 4 g/mm of cyclophosphamide and daily filgrastim. As a conditioning regimen, patients received carmustine, cytosine arabinoside, etoposide, and melphalan. Posttransplantation therapy included rabbit antithymocyte, prednisone, intravenous cyclosporine, and weekly intravenous immunoglobulin. Five nonfatal events occurred during the mobilization period. During the early transplantation period, fever, sepsis, symptomatic cytomegalovirus reactivation, and urinary tract infections occurred. Between 2 and 4 months, 2 documented herpes zoster infections occurred. In comparison, the toxicity profile encountered with HDC was much less severe and no chemotherapy toxic effects occurred between 2 and 4 months. Another study of intense T-cell depletion followed by HSCT concluded that there were serious toxic effects without clinical disease progression prevention: " . . . of [their] 9 patients who deteriorated, 7 became worse within the first 6 months . . . of transplantation."[20]

When describing the effects of a new therapy, disability scale analyses are insufficient endpoints, as they do not always parallel disease activity.[22,23] Here we provide longitudinal data on the long-term QOL effect of HDC. Our patients' baseline data support previous reports that patients with MS have a reduced QOL.[24] Although this is an open-labeled trial that may potentially confound QOL assessment, after this single intervention, these patients reported improvement in multiple QOL parameters as measured in this group's physical and mental composite health averages of score changes. The analyses at 1 year and last follow-up indicate that HDC's effects are durable and unrelated to the transient chemotherapy-induced anti-inflammatory state associated with neutropenia. Importantly, increases in QOL parameters were not limited to those who had a decrease in their EDSS scores. Additionally, a clinically significant reduction in the FSS score[25] was achieved in the majority of measured patients.

For many patients with MS, current therapy does not stop disease progression. These patients with advanced refractory MS of long duration underwent a single intervention, HDC. This 4-day infusion was extremely well tolerated. This group not only had EDSS score stabilization but overall had both increased functionality inde-

pendent of further remittive therapy and QOL improvement. Further studies are necessary to determine the most appropriate patients for this treatment.

Published Online: August 14, 2006 (doi:10.1001/archneur.63.10.noc60076).
Accepted for Publication: May 24, 2006.
Correspondence: Douglas E. Gladstone, MD, Division of Oncology, Stony Brook University Health Sciences Center, T17-080, Stony Brook, NY 11794 (dgladstone@notes.cc.sunysb.edu).
Author Contributions: *Study concept and design:* Gladstone. *Acquisition of data:* Gladstone, Zamkoff, Krupp, Peyster, Sibony, Christodoulou, Locher, and Coyle. *Analysis and interpretation of data:* Gladstone, Krupp, Peyster, Christodoulou, and Coyle. *Drafting of the manuscript:* Gladstone, Krupp, Peyster, Sibony, Christodoulou, Locher, and Coyle. *Critical revision of the manuscript for important intellectual content*: Gladstone, Locher, and Coyle. *Statistical analysis:* Gladstone and Coyle. *Obtained funding:* Gladstone. *Administrative, technical, and material support:* Gladstone and Locher. *Study supervision:* Gladstone, Krupp, Peyster, and Coyle.
Acknowledgment: We give special thanks to Ann Prestrud, MPH, for help in obtaining the investigational new drug and to June Giardelli, NP, for help in maintaining the investigational new drug.

REFERENCES

1. Karp CL, van Boxel-Dezaire AH, Byrnes AA, Nagelkerken L. Interferon-beta in multiple sclerosis: altering the balance of interleukin-12 and interleukin-10? *Curr Opin Neurol*. 2001;14:361-368.
2. Bjartmar C, Trapp BD. Axonal and neuronal degeneration in multiple sclerosis: mechanisms and functional consequences. *Curr Opin Neurol*. 2001;14:271-278.
3. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med*. 2000;343:938-952.
4. Goodin DS, Frohman EM, Garmany GP Jr, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines [erratum appears in *Neurology*. 2002;59:480]. *Neurology*. 2002;58:169-178.
5. Prestrud AA, Gladstone DE. Quality of life after high-dose cyclophosphamide in patients with severe autoimmune diseases. *J Eval Clin Pract*. 2005;11:411-416.
6. Gladstone DE, Prestrud AA, Brannagan TH III. High-dose cyclophosphamide results in long-term disease remission with restoration of a normal quality of life in patients with severe refractory chronic inflammatory demyelinating polyneuropathy. *J Peripher Nerv Syst*. 2005;10:11-16.
7. Gladstone DE, Brannagan TH III, Schwartzman RJ, Prestrud AA, Brodsky I. High dose cyclophosphamide for severe refractory myasthenia gravis. *J Neurol Neurosurg Psychiatry*. 2004;75:789-791.
8. Gladstone DE, Prestrud AA, Pradhan A, et al. High-dose cyclophosphamide for severe systemic lupus erythematosus. *Lupus*. 2002;11:405-410.
9. Brodsky RA, Sensenbrenner LL, Smith BD, et al. Durable treatment-free remission after high-dose cyclophosphamide therapy for previously untreated severe aplastic anemia. *Ann Intern Med*. 2001;135:477-483.
10. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." *Ann Neurol*. 2005;58:840-846.
11. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36), I: conceptual framework and item selection. *Med Care*. 1992;30:473-483.
12. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol*. 1988;45:435-437.
13. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001;50:121-127.
14. Saccardi R, Mancardi GL, Tyndall A. Autologous hematopoietic stem cell transplantation in multiple sclerosis. In: *A Report of the European Blood and Marrow Transplantation Group (EBMT)*. Atlanta, Ga: American Society of Hematology; 2005.
15. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. *Neurology*. 2004;63:S28-S32.
16. Openshaw H, Stuve O, Antel JP, et al. Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. *Neurology*. 2000;54:2147-2150.
17. Brodsky RA, Petri M, Smith BD, et al. Immunoablative high-dose cyclophosphamide without stem-cell rescue for refractory, severe autoimmune disease. *Ann Intern Med*. 1998;129:1031-1035.
18. Hough RE, Snowden JA, Wulffraat NM. Haemopoietic stem cell transplantation in autoimmune diseases: a European perspective. *Br J Haematol*. 2005;128:432-459.
19. Burt RK, Cohen B, Rose J, et al. Hematopoietic stem cell transplantation for multiple sclerosis. *Arch Neurol*. 2005;62:860-864.
20. Samijn JP, te Boekhorst PA, Mondria T, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2006;77:46-50.
21. Saccardi R, Mancardi GL, Solari A, et al. Autologous HSCT for severe progressive multiple sclerosis in a multicenter trial: impact on disease activity and quality of life. *Blood*. 2005;105:2601-2607.
22. Merkies IS, Schmitz PI, van der Meche FG, et al. Quality of life complements traditional outcome measures in immune-mediated polyneuropathies. *Neurology*. 2002;59:84-91.
23. Strand V, Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P. Outcome measures to be used in clinical trials in systemic lupus erythematosus. *J Rheumatol*. 1999;26:490-497.
24. Lobentanz IS, Asenbaum S, Vass K, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand*. 2004;110:6-13.
25. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology*. 2003;60:1923-1930.