High-Dose Cyclophosphamide for Moderate to Severe Refractory Multiple Sclerosis

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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). Two of 11 patients had a single enhancing lesion at baseline; these lesions resolved after high-dose cyclophosphamide treatment. At 12 months, 1 patient showed 1 new enhancing lesion without a corresponding high-intensity T2-weighted or fluid-attenuated inversion recovery signal. 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.

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Multiple sclerosis (MS) is a major disabling neurologic disease of young adults and represents the most common immune-mediated inflammatory and demyelinating disorder of the central nervous system. The disability that MS produces is underscored by nearly 50% of patients who will require ambulatory aids within 15 years after disease onset. 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.

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 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. 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 Admin-
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>MS Subtype</th>
<th>Disease Duration, y</th>
<th>Baseline EDSS Score</th>
<th>IM INF-β1a, y</th>
<th>SC INF-β1b, y</th>
<th>SC IFN-β1a, y</th>
<th>Glatiramer Acetate, y</th>
<th>IVlg</th>
<th>Mitoxantrone Hydrochloride, mg/mm</th>
<th>Other</th>
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<tr>
<td>1/F/45</td>
<td>RR</td>
<td>15.4</td>
<td>5.0</td>
<td>+</td>
<td>−</td>
<td>0.7</td>
<td>0.75</td>
<td>2.0</td>
<td>−</td>
<td>−</td>
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<td>2/M/40</td>
<td>RR</td>
<td>17.7</td>
<td>4.0</td>
<td>+</td>
<td>1.5</td>
<td>2.3</td>
<td>0.25</td>
<td>+</td>
<td>92</td>
<td>−</td>
</tr>
<tr>
<td>3/F/48</td>
<td>SP</td>
<td>5.8</td>
<td>8.0</td>
<td>+</td>
<td>5.5*</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>65</td>
</tr>
<tr>
<td>4/F/46</td>
<td>SP</td>
<td>17.1</td>
<td>6.5</td>
<td>+</td>
<td>1.0</td>
<td>−</td>
<td>6.20*</td>
<td>−</td>
<td>72</td>
<td>Azathioprine, 1.5 y; MTX, 18 g/wk for 10 mo</td>
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<td>5/F/40</td>
<td>SP</td>
<td>22.0</td>
<td>6.5</td>
<td>+</td>
<td>7.2*</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<td>−</td>
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<td>+</td>
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<td>8.4</td>
<td>−</td>
<td>+</td>
<td>48</td>
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<td>SP</td>
<td>19.2</td>
<td>7.0</td>
<td>+</td>
<td>1.0</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>54</td>
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<td>+</td>
<td>2.0</td>
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<td>0.50*</td>
<td>−</td>
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<td>−</td>
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<tr>
<td>9/F/28</td>
<td>RR</td>
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<td>5.5</td>
<td>+</td>
<td>5.2</td>
<td>1.0*</td>
<td>−</td>
<td>−</td>
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<td>29.0</td>
<td>7.5</td>
<td>+</td>
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<td>11.5*</td>
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<td>−</td>
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<tr>
<td>11/F/27</td>
<td>RR</td>
<td>5.8</td>
<td>6.0</td>
<td>+</td>
<td>5.5*</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<td>4.5</td>
<td>+</td>
<td>4.0</td>
<td>2.25*</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>13/F/20</td>
<td>RR</td>
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<td>6.5</td>
<td>+</td>
<td>0.6*</td>
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<td>0.83</td>
<td>+</td>
<td>75</td>
<td>Cyclophosphamide, 1 g/mo for 2 y</td>
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</table>

Abbreviations: EDSS, Expanded Disability Status Scale; IM, intramuscular; INF, interferon; IVlg, 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.

Intration—approved disease-modifying therapies. For patients with relapsing-remitting 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 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. 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.

### 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-
tion (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.

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.
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 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
verse cardiac history, prior radiation, or chemotherapy. However, patients with ad-
2% and rises to 5% when doses of mitoxantrone hydro-
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.5,6 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.7 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 ambula-
tion (the major determinant of the EDSS score), 3 pa-
tients improved to full ambulatory status, walking with-
out an aid or rest for 500 m; for urinary function, 5 patients (including 2 patients with previous incontinence) ex-
perienced full resolution of urinary symptoms; and for vi-
sual function, patients’ performance improved in sepa-
ately measured parameters of visual acuity and color perception.

Baseline radiographic imaging revealed a high num-
ber of lesions consistent with this cohort’s disease sever-
ity. 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 de-
veloped 1 new enhancing lesion that was not associated with a T2-enhanced or fluid-attenuated inversion recov-
ery signal.

Currently, the only Food and Drug Administration–
approved chemotherapy for MS is mitoxantrone. Neutro-
penia 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 hydro-
chloride exceed 100 mg/mm. However, patients with ad-
verse cardiac history, prior radiation, or chemotherapy