Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis:

Final report of the Northeast Cooperative Multiple Sclerosis Treatment Group

H.L. Weiner, MD; G.A. Mackin, MD; E.J. Orav, PhD; D.A. Hafler, MD; D.M. Dawson, MD; Y. LaPierre, MD; R. Herndon, MD; J.R. Lehrich, MD; S.L. Hauser, MD; A. Turel, MD; M. Fisher, MD; G. Birnbaum, MD; J. McArthur, MD; R. Butler, MD; M. Moore, MD; B. Sigsbee, MD; A. Safran, MD; and the Northeast Cooperative Multiple Sclerosis Treatment Group*

Article abstract—Previous studies reported that a 2- to 3-week course of IV cyclophosphamide plus adrenocorticotropic hormone (ACTH) induction can temporarily halt progressive MS for a period of 12 months in the majority of patients treated, after which reprogression occurs. The Northeast Cooperative Multiple Sclerosis Treatment Group was formed to determine whether outpatient pulse cyclophosphamide therapy could affect reprogression and whether there were differences between a modified induction regimen and the previously published regimen. Two hundred fifty-six progressive MS patients were randomized into four groups to receive IV cyclophosphamide/ACTH via the previously published versus a modified induction regimen, with or without outpatient IV cyclophosphamide boosters (700 mg/m^2 every other month for 2 years). There were blinded evaluations performed every 6 months. Results demonstrate that (1) there were no differences between the modified and the published induction regimens either in terms of initial stabilization or subsequent progression; (2) without boosters, the majority of patients continued to progress; and (3) in patients receiving boosters, there was a statistically significant benefit at 24 months and 30 months ($p = 0.04$). Time to treatment failure after 1 year was also significantly prolonged in the booster versus the nonbooster group ($p = 0.03$). Age was the most important variable that correlated with response to therapy in that amelioration of disease progression occurred primarily in patients 40 years of age or younger. Boosters had a significant benefit on time to treatment failure in patients ages 18 to 40, $p = 0.003$, but not in patients ages 41 to 55, $p = 0.97$. In addition, patients with primary progressive MS had a poorer prognosis at 12 months than patients with secondarily progressive MS ($p = 0.04$). Our findings (1) support a role for immunosuppression in the treatment of MS, (2) begin to identify variables that may explain differences between studies of immunosuppression with cyclophosphamide in progressive MS, and (3) suggest that intermittent pulse therapy is an important method for the treatment of progressive MS and perhaps for earlier stages of MS as well.

NEUROLOGY 1993;43:910-918

Multiple sclerosis is an inflammatory disease of the central nervous system of presumed autoimmune etiology. There are a number of immune abnormalities in MS, including loss of suppressor influences and activated T and B cells both in the CNS and the peripheral blood.[1] The design of the majority of immunotherapeutic approaches studied over the past 20 years has been to suppress the immune system in patients with MS with both antigen-specific and antigen-nonspecific suppression.[2]

Based on uncontrolled reports which suggested that intensive immunosuppression with short-term administration of cyclophosphamide plus corticosteroids affected the course of progressive and relapsing-remitting MS,[3-7] in 1980, Boston investigators undertook a randomized trial of high-dose

* For list of centers, see Appendix on page 918.

From the Multiple Sclerosis Unit of the Center for Neurologic Diseases, Division of Neurology, Department of Medicine (Drs. Weiner, Hafler, Mackin, and Dawson), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; Department of Biostatistics, Harvard School of Public Health (Dr. Orav), Boston, MA; Montreal Neurologic Institute (Dr. LaPierre), Montreal, PQ, Canada; Massachusetts General Hospital (Drs. Lehrich and Hauser), Boston, MA; Strong Memorial Hospital (Dr. Herndon), Rochester, NY; Geisinger Medical Center (Dr. Turel), Danville, PA; University of Minnesota Hospital (Dr. Birnbaum), Minneapolis, MN; Worcester Memorial Hospital (Dr. Fisher), Worcester, MA; Johns Hopkins Medical Center (Dr. McArthur), Baltimore, MD; Eastern Maine Medical Center (Dr. Sigsbee), Bangor, ME; Framingham Union Hospital (Dr. Safran), Framingham, MA; and Emerson Hospital and Boston University School of Medicine (Drs. Butler and Moore), Concord, MA.

Supported by a grant from the National Multiple Sclerosis Society.

Presented in part at the 43rd (Boston, MA) and 44th (San Diego, CA) annual meetings of the American Academy of Neurology, April 1991 and May 1992.

Received March 16, 1992. Accepted for publication in final form September 14, 1992.

Address correspondence and reprint requests to Dr. Howard L. Weiner, Center for Neurologic Diseases, Longwood Medical Research Center, 221 Longwood Avenue, Boston, MA 02115-5817.

intravenous cyclophosphamide plus adrenocorticotropic hormone (ACTH) versus ACTH alone or a plasma exchange regimen in 58 patients with progressive MS. Results demonstrated that a 2- to 3-week course of IV cyclophosphamide plus ACTH could halt the progression of chronic progressive MS for a 1-year period in approximately 75% of the 20 patients treated.[8] Continued follow-up demonstrated that of those patients who benefitted from treatment either by stabilization or improvement, the majority began reprogressing between 12 and 18 months after the initial treatment.[9] However, there were patients whose reprogression began 6 to 9 months after treatment or as long as 3 years after treatment. This study supported the positive results obtained by earlier investigators who had treated MS patients with cyclophosphamide in combination with corticosteroids.[3-7]

Following publication of the Boston results in 1983, there was heightened interest in the potential use of immunosuppression with cyclophosphamide in progressive MS. The Northeast Cooperative Multiple Sclerosis Treatment Group, formed in 1984 to further study the effect of cyclophosphamide on the course of progressive MS, allowed multiple centers to treat patients according to a standardized protocol and to treat sufficient numbers of patients to answer the clinical questions raised in the protocol. The Treatment Group had several options for the next questions to investigate regarding the use of cyclophosphamide in progressive MS, including whether concomitant steroids were required and whether the original study should be repeated. The group decided that the most important question was whether a form of intermittent outpatient pulse cyclophosphamide therapy, that has become standard for diseases such as lupus nephritis,[10] could affect subsequent reprogression in progressive MS patients treated with cyclophosphamide/ACTH induction. In addition, we wished to investigate whether a modified regimen that required shorter hospitalization, or that could be administered on an outpatient basis, was as efficacious as the published regimen.

Methods. *Patient population.* A total of 261 eligible patients with progressive MS were randomized among four treatment groups. This number excludes 26 patients with no data who were randomized but not treated because of subsequent issues concerning eligibility. An additional five patients were removed from all analyses because no data from the initial examination were submitted, making it impossible to assess progress (two of the five patients were from arm 1, and one patient was from each of the other arms). The remaining 256 patients provided data for analysis. The original study protocol called for 75 patients per arm in order to detect 15% stabilization or improvement on the nonbooster arms at 3 years compared with 40 to 45% stabilization or improvement on the booster arms, with 95% power and 5% type I error.

Patients had clinically definite MS according to the Schumacher criteria with at least 1-point worsening on the Kurtzke Disability Status Scale (DSS) or Ambulation Index (AI) in the 12 months prior to entry. Screening by history and laboratory tests where appropriate was carried out before entry to rule out other diagnoses such as systemic lupus erythematosus and Sjögren's syndrome. Worsening prior to entry was determined by examination of patients (change in AI) or history and record review if changes involved clear worsening on DSS (eg, need for the use of a cane). At entry, patients were classified as having primary progressive MS (progressive MS from onset of disease without a history of relapses or remissions) or progressive MS that evolved after a prior relapsing-remitting course. Patients were between the ages of 18 and 55 at randomization and had a DSS of 3 through 6B (6B = Expanded Disability Status Scale [EDSS] of 6.5, requiring bilateral support for ambulation) or a DSS of 7 that occurred due to disease progression in the previous 2 months.

The study was designed to include participation of both academic institutions and private neurologic practices since the treatment involved readily available drugs. Prior to initiating the trial and at periodic times during the course of the study, investigator meetings were held to assure standardization of neurologic assessments and conduct of the trial. A total of 28 participating groups started the trial, although nine centers were removed when the majority of their data remained incomplete. The remaining 21 centers enrolled patients that were randomized centrally at the Brigham and Women's Hospital in Boston. Review of initial evaluations, verification of eligibility, checks for consistency of data, and maintenance of the database were performed centrally by neurologists (G.A.M. and H.L.W.) at the Brigham and Women's Hospital.

Treatment regimens. There were four treatment groups. All patients received induction with cyclophosphamide/ACTH in the hospital. Groups 1 and 2 were randomized to receive treatment according to the previously published regimen: 125 mg cyclophosphamide intravenously four times a day over 8 to 18 days until the white blood cell count fell below 4,000/mm^3 plus IV ACTH.[8] Groups 3 and 4 received a modified regimen in which cyclophosphamide at a dose of 600 mg/m^2 was given intravenously on days 1, 2, 4, 6, and 8. Patients on the modified regimen received IM ACTH over 14 days (40 units twice daily for 7 days, 40 units daily for 4 days, and 20 units daily for 3 days). Following induction in the hospital, patients in groups 2 and 4 received 700 mg/m^2 cyclophosphamide intravenously every 2 months for a 2-year period, whereas patients in groups 1 and 3 remained untreated.

Neurologic evaluation and conduct of the study. The protocol was approved by institutional review boards at each of the participating centers. After informed consent was obtained, patients were randomized centrally at the Brigham and Women's Hospital and hospitalized at their respective center. Individual randomization schemes were prepared for each center and kept at the Brigham and Women's Hospital, and assignment to an experimental group occurred at the time of randomization. Specifically, when a center identified a patient eligible for the study, they contacted the Brigham and Women's Hospital and were informed of the assigned treatment group. Two scoring systems were used to assess neurologic status: (1) DSS in which the sixth category was divided into 6A (unilateral support for ambulation) or 6B (bilateral support for ambulation)—these categories are equivalent to 6.0 and 6.5 on the EDSS; and (2) the AI.[8] Patients were evaluated on admission to the hospital and at 6-month intervals for 3 years thereafter. In addition, an evaluation was performed whenever a patient reported worsening of the condition.

Neurologic evaluations were performed in a single-blind fashion by the examining neurologist. For most centers, except the Brigham and Women's Hospital, there was a single examining neurologist for each patient and this individual was also the treating physician. All patients experienced alopecia, which was evident at the 6-month evaluation. By 12 months there was no alopecia, and the dose of cyclophosphamide boosters did not result in hair loss; thus, a blinded examination could be carried out during the entire study. Although formal interrater variability was not assessed, all examining neurologists were familiar with and had experience using the scales, and detailed discussion of rating methods were carried out prior to and during the course of the study.

Statistical methods. This study was designed to answer two questions: (1) How does the administration of cyclophosphamide boosters in addition to induction (groups 2 and 4) compare with induction alone (groups 1 and 3), and (2) how does a modified cyclophosphamide regimen (groups 3 and 4) compare to the published regimen (groups 1 and 2)? To address these questions, three primary endpoints were chosen. Each of the endpoints was based on the following protocol-based definition of treatment failure: patients were treatment failures if they declined 1 point on the DSS and remained at that level for 2 months, were removed from follow-up for medical reasons related to treatment, or were removed from follow-up because of deviation from the protocol-prescribed treatment regimen. These last two components of failure were included so that we could analyze by intent to treat. A 1-point decline in the DSS included a change from 6A to 6B and from 6B to 7. In 13 instances (seven booster patients and six nonbooster patients), a patient declined 1 point, was not retreated, and recovered later in the study to be stable or improved. These patients were classified as treatment failures at the time of their decline for purposes of survival analysis. They were, however, included in calculations of percentage of patients improved or stable. All patients who were retreated either with steroids or immunosuppressive therapy remained failures for the rest of the study.

To assess early differences, the first endpoint compares patient groups at 12 months on the basis of failure versus stabilization or improvement. Those patients who were not treatment failures at 12 months were classified either as stable if their DSS was the same as at the start of treatment, or as improved if their DSS improved by 1 or more points. The Mantel-Haenszel trend test was used to compare patients on published induction to those on modified induction and to compare patients on boosters to those not on boosters.

The second endpoint assessed long-term efficacy and is identical in definition and in terms of analysis to the first, except that 24-month data are used to define failure, stabilization, and improvement. Time to first failure was the third endpoint, and allows analysis across the entire 3 years of follow-up. A proportional hazards survival model was used to compare patient groups, both before and after adjustment for baseline characteristics. Patients who withdrew from the study for nonmedical reasons are treated as censored in such an analysis, contributing information only until their time of withdrawal.

All analyses were repeated using 1-point changes on the AI to define failure, and for the first two endpoints, stability and improvement. Since these analyses produced very similar results to those based on DSS, we refer only occasionally to the comparative results. In addition to the three primary endpoints, we compared patient groups at each 6-month follow-up and used an ordinal logistic regression model to identify subgroups of patients more prone to stabilization and improvement.

When we identified a characteristic, such as age, that was related to booster efficacy, we divided the patients by median age into two subgroups and analyzed each subgroup separately for the effect of boosters using the Mantel-Haenszel trend test and the survival regression.

Table 1. Patient demographic and clinical characteristics

	No boosters	Boosters	Modified	Published
Sample size	129	127	139	117
Average age (±SD)	39.8 ± 8.1	40.3 ± 8.4	40.4 ± 8.1	39.6 ± 8.4
Sex: % women	60%	59%	60%	58%
Type of MS prior to onset of progression				
Relapse/remit	38%	35%	34%	38%
Relapse/prog.	36	36	40	31
Chronic onset	27	29	26	31
Prior treatment with ACTH, prednisone	88%	78%	81%	85%
Average age at onset	31.7 ± 7.5	31.3 ± 9.4	31.5 ± 8.5	31.6 ± 8.5
Disability score				
3-4	9%	14%	14%	9%
5	6	9	4	10
6A	44	33	40	37
6B	32	36	32	37
7	10	8	10	8
Average	5.9 ± 0.9	5.7 ± 1.1	5.8 ± 1.1	5.9 ± 0.8
Ambulation Index				
2-3	14%	20%	18%	16%
4-5	49	41	45	44
6-7	33	38	33	38
8	4	2	3	3
Average	4.9 ± 1.6	4.8 ± 1.5	4.7 ± 1.6	4.9 ± 1.5

Results. *Patient characteristics.* The four treatment groups were well matched with respect to age, sex, and duration of disease, type of MS before onset of progression, previous treatment with ACTH or prednisone, and initial DSS and AI. The majority of patients, 73%, required unilateral or bilateral support for ambulation (DSS of 6A or 6B). No significant differences were found on any of these measures (table 1). The four groups were followed to failure or censoring an average of 508 days, 510 days, 506 days, and 555 days. Patient accrual by center is shown in the Appendix.

During the course of the 3-year trial, 26 patients withdrew due to medical complications from treatment or due to problems with treatment. Those patients were treated as failures as of their dates of withdrawal and throughout the remainder of the study. Six of these failures were among patients not on boosters (two on arm 1 and four on arm 3), while 20 of the failures were among boosters patients (10 on arm 2 and 10 on arm 4). An additional 11 patients withdrew for reasons determined to be unrelated to treatment or disease, but all these patients had suffered disease progression and were therefore classified as failures for purposes of

Table 2. Percentages of patients who were stable/improved measured by the Kurtzke Disability Status Scale comparing arms receiving maintenance boosters and no maintenance boosters

	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
No boosters (groups 1 and 3)	75%	56%	46%	24%	17%	15%
Maintenance boosters (groups 2 and 4)	71%	55%	48%	38%	27%	20%
Significance level for a trend test comparing the two groups on the proportions of patients improved, stable, and worse	0.76	0.71	0.61	0.04	0.04	0.14

Ambulation Index shows similar significant differences at 24 months ($p = 0.04$) and at 30 months ($p = 0.03$).

survival analysis. Finally, 15 patients withdrew for nonmedical reasons during the first 6 months, and 12 or 13 during each subsequent 6-month follow-up without evidence of disease worsening. These patients stopped contributing information to the analysis as of the dates they withdrew. They were evenly distributed between the booster (n = 34) and nonbooster groups (n = 29).

Comparison of published versus modified induction. No differences in response were found between patients receiving the modified induction compared with those receiving the published induction. At 6 months, 22% were improved and 49% stable on modified induction compared with 24% improved and 52% stable on the published induction ($p = 0.43$). Twelve-month data showed 19% improved on the modified arm and 35% stable, versus 23% improved and 35% stable on the published arm ($p = 0.48$). At 2 years, 13% of modified-arm patients were improved and 17% were stable, versus 9% improved and 21% stable on the standard arm ($p = 0.91$). The time-to-failure analysis showed similar results with virtually coincidental survival curves and a nonsignificant difference ($p = 0.83$) between the two induction regimens. Similar results were obtained on calculations using the AI.

Comparison of maintenance boosters versus no boosters (table 2, figure 1). Maintenance boosters significantly slowed progression at 24 months ($p = 0.04$), although no improvement was noted at 12 months ($p = 0.71$) or through the use of survival analysis ($p = 0.18$). At 24 months, the booster arm showed 16% improved and 22% stable, compared with 9% improved and 15% stable on the nonbooster arm. Further analyses verified that the impact of boosters persisted at 30 months ($p = 0.04$) and could be replicated on the AI at both 24 months ($p = 0.04$) and 30 months ($p = 0.03$). Table 2 suggests that the impact of booster therapy does not begin until after the 18-month evaluation. We pursued this idea by repeating the survival analysis, treating booster therapy as a time-varying predictor whose impact begins at 1 year. Figure 1 shows the comparison of

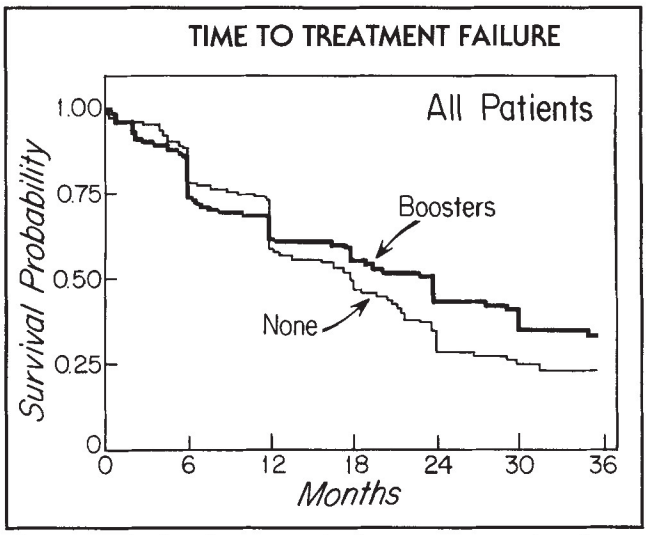

Figure 1. Kaplan-Meier survival curves comparing time to treatment failure in patients receiving bimonthly cyclophosphamide boosters with patients receiving no booster therapy. Percentage of individuals who were not treatment failures are plotted versus time. No significant difference was found (p = 0.18) over the entire course of follow-up, but in examining booster effects starting at 1 year, a significant benefit (p = 0.03) was detected.

time to failure with and without boosters. Boosters had significant impact ($p = 0.03$) on delaying reprogression after 1 year; this is consistent with previous observations that the average time to reprogression following cyclophosphamide/ACTH induction is approximately 18 months.[9] A similar survival analysis supported the finding using the AI to define failure ($p = 0.06$). The actual values of the DSS at the follow-up times are not given as they are misleading, since patients who fail either have no DSS value or have a value that reflects retreatment as well as the original randomized therapy. For this reason, we do not report or compare these values.

Comparison of different centers and identification of responsive subgroups. A large population of patients were treated at the Brigham and Women's

Table 3. Effect of treatment in younger (ages 18-40) versus older (ages 41-55) patients*

	Percentage of patients improved or stable					
	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo
Patients on boosters (n = 107)						
Young (n = 54)	81%	62%	57%	42%	40%	28%
Improved	30	28	26	23	24	18
Stable	51	34	31	19	16	10
Old (n = 53)	60%	47%	40%	34%	14%	12%
Improved	17	19	16	10	5	5
Stable	43	28	24	24	9	7
p value	0.02	0.13	0.10	0.18	0.01	0.05
Patients not on boosters (n = 113)						
Young (n = 53)	81%	60%	54%	23%	9%	9%
Improved	26	25	27	12	2	2
Stable	55	35	27	11	7	7
Old (n = 60)	70%	53%	38%	25%	25%	20%
Improved	18	11	8	6	7	4
Stable	52	42	30	19	18	16
p value	0.14	0.14	0.02	0.79	0.06	0.16

* Improved or stable defined by DSS; at 36 months, analysis involves 81 patients on boosters (40 young, 41 old) and 94 patients not on boosters (47 young, 47 old).

Hospital (85 of 256); some centers treated very small numbers of patients (eg, two). Thus, data were analyzed according to center size to determine whether treatment was differentially successful at the Brigham and Women's Hospital and at other centers. Since the primary finding of the study group was a slowing of progression at 24 and 30 months in patients receiving boosters, these two time points were the focus of analysis. At 24 and 30 months, a positive effect of boosters was observed both in the 85 patients treated at the Brigham and Women's Hospital and in the 145 patients treated at centers with only 8 to 21 patients ($p = 0.02$ at 24 months and $p = 0.04$ at 30 months). No effects of boosters were observed when centers with six or fewer patients were analyzed (n = 26).

We then performed analyses to determine whether there were any other characteristics that were prognostic of success and whether the effects of boosters were specific to a particular subgroup of patients. Because of our previous findings, the impact of boosters on the survival analysis was allowed to appear only after the first year of follow-up. We considered the following measures of clinical status at the beginning of treatment: DSS, AI, and *each of* the six functional status scales that focus on a specific locus of disability. We found that none of these predicted failure at 12 months, 24 months, or throughout the course of follow-up. However, patients who were chronic progressive from the onset of their MS had particularly poor prognosis at 12 months ($p = 0.04$). Over 55% of patients who were chronic progressive from onset had failed by 12 months, while only 41% of the other patients had failed. The type of MS at onset was not prognostic at 24 months or in the survival analyses. Similarly, previous treatment with ACTH or steroids did not alter prognosis.

The most striking finding, however, was that younger patients early in their disease were most likely to stabilize or improve. Since the median age of patients in the study was 41 years, the clinical course of patients above and below the median was analyzed. In addition to age, a number of other measures of "early in disease" were analyzed, including patients who had an early onset (chronic progression before age 32), patients who had a recent onset of chronic progression (within the past 7 years), and patients who were young and had recent onset (age less than 41 and chronic progression within the last 7 years). Table 3 shows analyses of patients ages 18 to 40 versus patients ages 41 to 55. Boosters are of greater benefit in younger patients (40% stable or improved at 30 months with boosters versus 9% without boosters, $p = 0.01$) than in older patients (14% stable or improved at 30 months with boosters versus 25% without boosters, $p = 0.27$). Furthermore, at 18 months, the percentage of patients improved or stable that did not receive boosters was also greater in younger than older patients (54% versus 38%, $p = 0.02$). Figure 2 shows the comparison of time to failure with and without boosters among patients ages 18 to 40 (n = 131) where there is a significant benefit from boosters after 1 year ($p = 0.003$), and among patients ages 41 to 55 (n = 125) where boosters had no impact ($p = 0.97$). Patients in the 18 to 40 and 41 to 55 age groups were also ana-

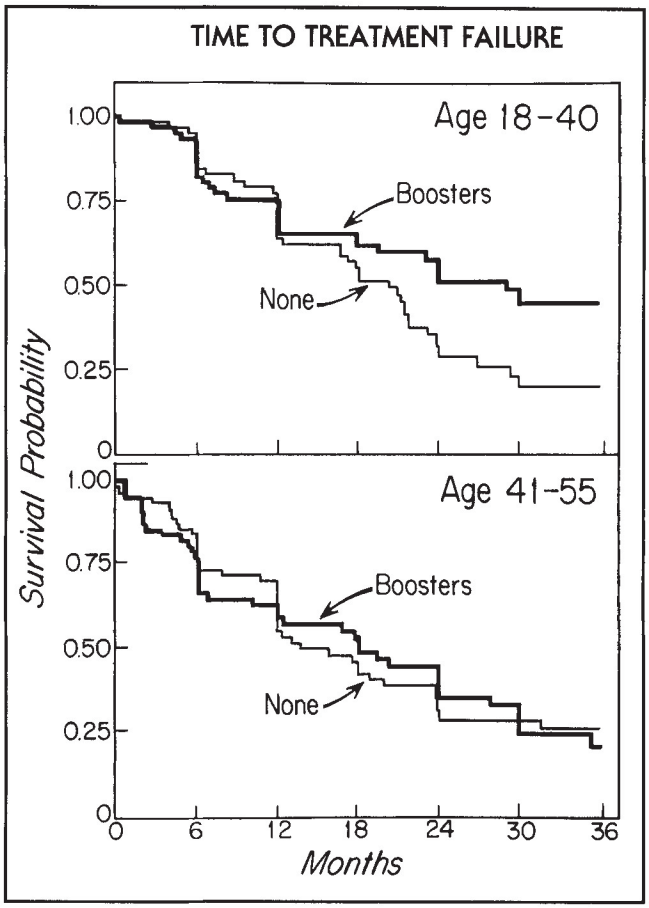

Figure 2. Kaplan-Meier survival curves comparing time to treatment failure in patients receiving cyclophosphamide boosters versus patients not receiving boosters. Percentage of individuals who were not treatment failures are plotted versus time. Survival comparisons are shown separately, first for patients less than the median age of 41 where boosters show a significant benefit (p = 0.003), and then for patients age 41 and above where boosters had no significant impact (p = 0.97).

lyzed to determine if a subcategory of patients responded (eg, ages 18 to 30 versus ages 30 to 40), but no differences were found. Patients who had recent onset of chronic progression (46% stable or improved at 24 months with boosters versus 22% without boosters, $p = 0.02$) responded better than those who had progressive disease for greater than 7 years (29% with boosters versus 27% without boosters, $p = 0.58$). Similarly, patients with early onset of progression responded better (39% stable or improved at 30 months with boosters versus 14% without boosters, $p = 0.01$) than those with onset after age 32 (16% with boosters versus 19% without boosters, $p = 0.87$). Of note is that in these analyses age was a confounding variable, as response to therapy was strongly associated with age.

To determine whether patients with a DSS of 7 on entry represented a different pattern of progression, these patients were analyzed separately. There was a total of 22 patients in this category. They were equally divided between those that received boosters (n = 10) and those that did not (n = 12). Even in this relatively small group of patients, similar findings were observed with these patients as with the study group as a whole. Specifically, patients with a DSS of 7 who received boosters did better than those who did not ($p = 0.04$ at 24 months). The effect was again seen primarily in younger patients (n = 15; $p = 0.04$ for booster efficacy at 24 months; $p = 0.04$ at 30 months) and not in older patients (n = 7; $p = 0.26$ at 24 months; all failures at 30 months).

Finally, to determine whether our decision to classify patients who withdrew for medical reasons as failures affected our results, we reclassified those patients as follows. If a patient had declined 1 point on the DSS they were still treated as a failure; if they withdrew while stable or improved, they were treated as censored. With this classification we found an even more significant benefit from boosters at 24 months, $p = 0.006$; at 30 months, $p = 0.004$; and at 36 months, $p = 0.024$. The survival analysis also showed a significant benefit due to boosters across time, $p = 0.027$, and after 1 year, $p = 0.028$.

Toxicities. All patients experienced complete scalp alopecia with induction. Fever and neutropenia (WBC, <700/mm^3) treated with antibiotics was associated with induction in 29 patients: 17 were culture negative, four were blood culture positive, four were associated with abscess, two with pneumonia, one viral upper respiratory infection, and one with an aseptic urinary tract infection. The majority occurred early in the study in the first 15 patients treated on 5 consecutive days on a modified regimen at a dose of 700 mg/m^2. Subsequently, dosing of 600 mg/m^2 was given over 8 days. Induction was also associated with the following toxicities: urinary tract infections (14), oral ulcers (1), candidal esophagitis (1), gross hematuria (3), and inappropriate ADH secretion (2). Booster therapy was associated with the following toxicities: recurrent urinary tract infections (4), chronic low WBC that did not recover to 4.0 (7), moderate to severe vomiting (16), and gross hematuria (1). Approximately one-third of patients experienced nausea alone with induction and on booster therapy. Menstrual abnormalities occurred in approximately half of the women that received induction or boosters. There were no deaths or secondary malignancies.

Discussion. The primary purpose of the Northeast Cooperative Treatment Group was to determine whether booster therapy every 2 months with cyclophosphamide at a dose of 700 mg/m^2 could alter disease progression in patients with MS. Although the results were not dramatic, there was a statistically significant benefit of boosters in the study group. Subset analysis demonstrated a strong correlation with age in the response to boosters and an age-related response in nonbooster patients at 18 months.

Because our purpose was not to repeat the 1983 Boston study, and because of the positive results reported with the induction regimen, all patients

received induction therapy to maximize the potential beneficial effects of boosters. This also allowed the physician to be blinded throughout the study.

The beneficial effects of booster treatment in the entire study group, although statistically significant, were relatively modest. We had hoped for a stabilization rate of greater than 50% at 2 years with boosters. There was, however, a strong association of stabilization with age, and younger patients had a stabilization rate that remained at 40% through 30 months. These findings confirm previous reports both by members of our group[9] and Hommes et al[6] that age is an important variable in responding to therapy.

Because all groups received induction therapy, the current study cannot be directly compared with the 1983 study in which the primary effect was a temporary halt in progression when the cyclophosphamide/ACTH group was compared to an ACTH-alone group. The degree to which an untreated or steroid- or placebo-treated group would have progressed compared with the treatment groups in the present study is unknown. It is also possible that if patients were left untreated, they may have done as well as the treatment groups, or that induction made patients worse and that the positive results of the booster infusions related to reversal of such negative effects, although we view these possibilities as unlikely.

Because the side effects associated with IV cyclophosphamide boosters made double blinding unfeasible, we did not give a placebo booster treatment. The examining physicians reported that they were unable to tell which patients received boosters. However, no formal assessment of blinding was done, and no attempt was made to blind the patients. It is thus possible that the benefit of boosters related to a "placebo effect" since half of the patients knew they were not being treated. Against this possibility is the fact that older patients did not respond to boosters whereas younger patients did. If the response to boosters was related to a placebo effect of receiving cyclophosphamide, it would imply that placebo effects are stronger in one age group than in the other.

Since the 1983 Boston study, other investigators have studied cyclophosphamide plus steroids in MS, using varying regimens.[11-17] Three studies involved booster or pulse therapy. In 1987, Myers et al[11] and Mickey et al[12] reported results of a preliminary open uncontrolled trial of IV cyclophosphamide pulses in chronic progressive MS. They measured clinical response and used measurements of immune function as guides to monthly escalating-dose cyclophosphamide treatments. Twelve of 14 patients improved or stabilized as determined by the DSS at 1 year, and there were correlations between immune measures and improvements on the neurologic examination, although the investigators reported a high rate of adverse side effects. In 1987, Goodkin et al[13] treated 27 progressive patients with high-dose IV cyclophosphamide plus steroids and compared them with 24 nonrandomized controls over 2 years. The study also included alternate-month IV cyclophosphamide booster therapy, similar to that given in the Northeast Cooperative Treatment Group, and at 12 months they found a difference in stabilization rates of cyclophosphamide/ACTH-treated patients as compared with controls (59% versus 17%), which persisted for 24 months (33% versus 4%). A trend favoring cyclophosphamide maintenance over nonmaintenance was present between 12 and 24 months, but was not statistically significant.[13] In 1988, Killian et al[14] reported on a pilot double-blind trial of monthly IV cyclophosphamide pulses in patients with relapsing-remitting MS. Eight patients received placebo and six patients received cyclophosphamide. The authors had previously found clinical benefit in an uncontrolled pilot study using monthly IV cyclophosphamide therapy at a dose of 750 mg/m^2 and the treated patients showed less frequent and less pronounced episodes than the placebo group, although these results were not significant given the small number of patients treated.

Three studies since the 1983 Boston report studied cyclophosphamide induction alone, without boosters, as compared to a placebo-treated group. Trouillas et al[16] reported similar results to the 1983 Boston study in an open study of 30 patients treated with cyclophosphamide/methylprednisolone versus a plasma exchange regimen versus a control group in which there was benefit in both treatment groups as compared with controls. Likosky et al,[17] in a 13-center Kaiser study, tested cyclophosphamide induction versus placebo for progressive MS in 42 patients in a double-blind study and reported no effect of cyclophosphamide. In contrast to the 1983 Boston study, the doses of cyclophosphamide were lower, there were no concomitant steroids given, and at 1 year 70% of the control group was stable; at 2 years EDSS change scores suggested more stability in the cyclophosphamide-treated than in the placebo group and the three most improved patients were in the cyclophosphamide group, although the sample size was too small to draw conclusions.[17]

In 1991, a Canadian study reported that a 2-week course of cyclophosphamide plus prednisone, given in a different regimen than we have employed and without boosters, did not affect progression over a 2-year period.[18] This carefully done and placebo-controlled study has been viewed as demonstrating that cyclophosphamide is ineffective in progressive MS. However, what is most dramatic in the Canadian study is the very high stabilization rate in the placebo group. In the Canadian study, 67% of 56 placebo-treated patients were stable at 2 years as compared with 22% in the 274 placebo-treated patients of the multicenter cyclosporine study of progressive MS[19] and 24% in the 129 patients in the nonbooster group of the present Northeast study. This high stabilization rate may have been related to different and less sensitive outcome measures than we and others have

employed for the study of progressive MS.[8,9,13,19] If little deterioration is found in controls, any improvement due to treatment will be difficult to detect. The Canadian study[18] defined worsening by a two-step change in EDSS. This is insensitive for progressive MS, especially in the EDSS range of 6.0 to 7.0. In this range, a one-step drop is dramatic: 6.0 = intermittent or constant unilateral assistance, 6.5 = the use of walker, and 7.0 = restricted to a wheelchair. The average disability of patients on entry to the Canadian study was nearly 6; thus, a patient who entered the trial using a cane who then worsened to using a walker, or who progressed from walker to wheelchair would have been classified as "stable." Other trials of immunosuppression in progressive MS defined worsening by a one-step increase in EDSS or AI.[8,9,13,19] Furthermore, in the Canadian study, an unusually large percentage of the cyclophosphamide-treated group (60%) and more than 50% of the study group as a whole had a primarily progressive illness unaccompanied by relapse. Purely progressive MS may represent a distinct subcategory of the disease,[20-22] and we have found in the present Northeast Cooperative Study that this subcategory has a particularly poor prognosis. Furthermore, these patients may also progress at a different rate. Despite these and other differences, the Canadian study did find a positive trend of immunosuppression in treated versus control patients at 12 months.[23] The results of the Canadian study must be reconciled with other studies of cyclophosphamide induction in MS in that it failed to show effects reported by others.[24] It appears that outcome measures chosen, the large proportion of primary progressive patients treated, and the age of patients treated may account for the differences.

It should be emphasized that disease progression in our nonbooster group and in the older patients as measured by treatment failure (figures 1 and 2) is quite similar to that in the multicenter cyclosporin A trial studying a nontreated placebo group. In both studies, (1) all groups continued to progress, and (2) positive effects appeared after the first year as also reported in the Kaiser study.[17] These findings have implications for future trials of immunosuppression in that the response of some progressive patients to immunosuppression may be a delayed effect that appears only after the first year of therapy.

We believe the results of the present study provide important information for the clinical investigation of immunosuppressive treatment for MS. First, short-term immunosuppression is not a lasting solution for progressive MS and, perhaps, for earlier stages of MS as well. MRI studies corroborate the clinical impression that a form of maintenance therapy is needed in MS, since MS lesions occur far more frequently than do clinical events and these lesions may occur even more frequently in progressive patients.[20-22] Second, maintenance immunosuppression of the type we employed has an ameliorating effect on progressive MS, although it clearly does not stop progression in all or even the majority of patients. Clinical investigation of immunosuppression in MS is warranted, especially using less toxic treatment regimens in earlier stages of disease. Third, age may be a crucial factor in response to therapy. The average age of patients treated in the 1983 Boston study was 30 years, whereas it was 40 years in the Canadian study, 40 years in the multicenter cyclosporine study, and 40 years in the current report. The age effect we have observed may represent disease duration with the accumulation of lesions that are no longer reversible, the establishment of irreversible immune- or nonimmune-mediated degeneration in the CNS, or both. Thus, differences between the results of various clinical trials may relate to variables that define patient subgroups. Prospective randomization for factors such as age, primary or secondarily progressive MS, and genetic background (eg, HLA types) may be crucial for defining which populations respond to a particular therapy. Immunologic measures may also help to define responding subgroups,[25,26] and we have obtained preliminary data suggesting certain immune measures may be linked to response to cyclophosphamide therapy.[26]

We emphasize that cyclophosphamide has limitations as a therapeutic agent in MS because of potential toxicity and nonspecific mode of action. We, and others, have studied its use in MS over the past 15 years and, based on past studies and the results obtained in the current study, we believe that the most appropriate way to administer cyclophosphamide is in a pulse booster program similar to what has become standard therapy for lupus nephritis where pulse intravenous cyclophosphamide reduces the risk of end-stage renal failure with few serious complications.[10] We currently are investigating what we believe to be maximal doses of pulse cyclophosphamide by giving it monthly in combination with methylprednisolone at doses designed to produce a leukopenia. Such treatment protocols are reserved for younger, actively progressive patients who have not responded to steroid treatments and for selected older patients to determine if they will respond to a more intensive booster regimen than employed in the present study. In most instances, we now start cyclophosphamide pulses after induction with intravenous methylprednisolone and in some instances without induction. Thus, patients do not suffer alopecia, initial profound drop in white blood cell count, or complications associated with induction and they can receive treatment solely as an outpatient. We are studying this more intensive outpatient booster therapy using a regimen where the drug is given monthly for a year, every 6 weeks for a second year, and then every 2 months for the third.[27] The degree to which patients reprogress after discontinuation of therapy, the length of time pulse cyclophosphamide can be safely given and tolerated by the patient, and the degree to which stabilization can be achieved with pulse methylprednisolone alone remain to be determined.

We believe the decision to use cyclophosphamide as a form of therapy for patients with MS remains a question to be answered by individual treating neurologists on a case-by-case basis. Although the drug has an ameliorating effect on the course of disease in some MS patients, its use is limited by its toxicity. Less toxic and more immune-specific therapies are required for MS, and such therapies should be initiated as early as possible in the disease. Toward this end, we and others are involved in the study of new treatments for MS including monoclonal antibodies, beta interferon, copolymer, oral tolerization to myelin antigens, T-cell receptor therapy, and potentially less toxic, commonly available immunosuppressive agents such as methotrexate.

Appendix. Patient accrual by center

Brigham and Women's Hospital	Boston, MA	85
Montreal Neurologic Institute	Montreal, Quebec	21
Massachusetts General Hospital	Boston, MA	18
Strong Memorial Hospital	Rochester, NY	17
Geisinger Medical Center	Danville, PA	15
University of Minnesota Hospital	Minneapolis, MN	14
Worcester Memorial Hospital	Worcester, MA	14
Johns Hopkins Medical Center	Baltimore, MD	11
Eastern Maine Medical Center	Bangor, ME	10
Framingham Union Hospital	Framingham, MA	10
Emerson Hospital	Concord, MA	9
Buxmont Neurological Associates	Sellersville, PA	8
Kennedy Memorial Hospital	Voorhees, NJ	6
Boston University Medical Center	Boston, MA	4
St. Vincent's Hospital	Worcester, MA	4
Beverly Hospital	Beverly, MA	2
Chevy Chase Neurological Associates	Chevy Chase, MD	2
Episcopal Hospital	Philadelphia, PA	2
Lehigh Valley Medical Center	Allentown, PA	2
Mecklenburg Neurological Associates	Charlotte, NC	2
Warwick Neurological Associates	Warwick, RI	2
	Total:	256

Acknowledgments

We thank Amy Hostetter for help in preparation of the manuscript. We are especially grateful to Lynn Stazzone, RN, who supervised administration of booster therapy at the Brigham and Women's Hospital.

References

1. Hafler DA, Weiner HL. MS: a CNS and systemic autoimmune disease. Immunol Today 1989;10:104-107.
2. Weiner HL, Hafler DA. Immunotherapy of multiple sclerosis. Ann Neurol 1988;23:211-222.
3. Hommes OR, Prick JJG, Lamers KJB. Treatment of the chronic progressive form of multiple sclerosis with a combination of cyclophosphamide and prednisone. Clin Neurol Neurosurg 1975;78:59-73.
4. Gonsette RE, Demonty L, Delmotte P. Intensive immunosuppression with cyclophosphamide in multiple sclerosis: follow-up of 100 patients for 2-6 years. J Neurol 1977;214:173-181.
5. Hommes OR, Lamers KJB, Reekers P. Effect of intensive immunosuppression on the course of chronic progressive multiple sclerosis. J Neurol 1980;223:177-190.
6. Hommes OR, Lamers KJB, Reekers P. Prognostic factors in intensive immunosuppressive treatment of chronic progressive MS. In: Bauer HJ, Poser S, Ritter G, eds. Progress in multiple sclerosis research. Berlin: Springer Verlag, 1980:396-400.
7. Gonsette RE, Demonty L, Delmotte P. Intensive immunosuppression with cyclophosphamide in remittent forms of multiple sclerosis: a follow-up of 134 patients for 2-10 years. In: Bauer HJ, Poser S, Ritter G, eds. Progress in multiple sclerosis research. Berlin: Springer Verlag, 1977:401-406.
8. Hauser SL, Dawson DM, Lehrich JR, et al. Intensive immunosuppression in progressive multiple sclerosis: a randomized, three-arm study of high-dose cyclophosphamide, plasma exchange, and ACTH. N Engl J Med 1983;308:173-180.
9. Carter JL, Hafler DA, Dawson DM, Orav J, Weiner HL. Immunosuppression with high-dose IV cyclophosphamide and ACTH in progressive multiple sclerosis: cumulative 6-year experience in 164 patients. Neurology 1988;38(suppl 2):9-14.
10. Balow JE, Austin HA, Tsokos GC, Antonovych TT, Steinberg AD, Klippel JH. Lupus nephritis. Ann Intern Med 1987;106:79-94.
11. Myers LW, Fahey JL, Moody DJ, Mickey MR, Frane MV, Ellison GW. Cyclophosphamide "pulses" in chronic progressive multiple sclerosis. Arch Neurol 1987;44:828-832.
12. Mickey MR, Ellison GW, Fahey JL, Moody DJ, Myers LW. Correlation of clinical and immunological states in multiple sclerosis. Arch Neurol 1987;44:371-375.
13. Goodkin DE, Plencner S, Palmer-Saxerud J, Teetzen M, Hertsgaard D. Cyclophosphamide in chronic progressive multiple sclerosis: maintenance vs. nonmaintenance therapy. Arch Neurol 1987;44:823-827.
14. Killian JM, Bressler RB, Armstrong RM, Huston DP. Controlled pilot trial of monthly intravenous cyclophosphamide in multiple sclerosis. Arch Neurol 1988;45:27-30.
15. Mauch E, Kornhuber HH, Pfrommer U, Hahnel A, Laufen H, Krapf H. Effective treatment of chronic progressive multiple sclerosis with low-dose cyclophosphamide with minor side-effects. Eur Arch Psychiatry Neurol Sci 1989;238:115-117.
16. Trouillas P, Neuschwander Ph, Nighoghossian N, Adeleine P, Tremisi P. Immunosuppression intensive dans la sclerose en plaques progressive etude ouverte comparant trois groupes: cyclophosphamide, cyclophosphamide-plasmapheres et temoins resultats a trois ans. Rev Neurol (Paris) 1989;145:5:369-377.
17. Likosky WH, Fireman B, Elmore R, et al. Intense immunosuppression in chronic progressive multiple sclerosis: the Kaiser study. J Neurol Neurosurg Psychiatry 1991;54:1055-1060.
18. The Canadian Cooperative Multiple Sclerosis Study Group. The Canadian Cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. Lancet 1991;337:442-446.
19. The Multiple Sclerosis Study Group. Efficacy and toxicity of cyclosporine in chronic progressive multiple sclerosis: a randomized, double-blinded, placebo-controlled clinical trial. Ann Neurol 1990;27:591-605.
20. Thompson AJ, Kermode AG, MacManus DG. Patterns of disease activity in multiple sclerosis: clinical and magnetic resonance imaging study. Br Med J 1990;300:631-634.
21. Thompson AJ, Kermode AG, Loicks D. Major differences in the dynamics of primary and secondary progressive multiple sclerosis. Ann Neurol 1991;29:53-62.
22. Olerup O, Hillert J, Fredrikson S. Primarily chronic progressive and relapsing/remitting multiple sclerosis: two immunogenetically distinct disease entities. Proc Natl Acad Sci U S A 1989;6:7113-7117.
23. Weiner HL, Hauser SL, Dawson DM, Hafler DA, Mackin GA, Orav EJ. Cyclophosphamide and plasma exchange in multiple sclerosis. Lancet 1991;337:1033-1034.
24. Noseworthy JN, Vandervoort MK, Penman M, et al. Cyclophosphamide and plasma exchange in multiple sclerosis. Lancet 1991;337:1540-1541.
25. Sharief MK, Hentges R. Association between tumor necrosis factor-alpha and disease progression in patients with multiple sclerosis. N Engl J Med 1991;325:467-472.
26. Hafler DA, Orav J, Gertz R, Stazzone L, Weiner HL. Immunologic effects of cyclophosphamide/ACTH in patients with chronic progressive multiple sclerosis. J Neuroimmunol 1991;32:149-158.
27. Hohol MJ, Mackin GA, Dawson DM, Hafler DA, Khoury SJ, Stazzone L, Weiner HL. Pilot study of three-year intermittent pulse cyclophosphamide/methylprednisolone therapy in multiple sclerosis [abstract]. Ann Neurol 1992;32:256-257.