FAILURE OF CYTARABINE IN PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

COLIN D. HALL, M.B., CH.B., URANIA DAFNI, SC.D., DAVID SIMPSON, M.D., DAVID CLIFFORD, M.D., PATRICIA E. WETHERILL, M.D., BRUCE COHEN, M.D., JUSTIN MCARTHUR, M.B., B.S., M.P.H., HARRY HOLLANDER, M.D., CONSTANTIN YAINNOUTSOS, PH.D., EUGENE MAJOR, PH.D., LINDA MILLAR, B.S., JOSEPH TIMPONE, M.D., AND THE AIDS CLINICAL TRIALS GROUP 243 TEAM*

ABSTRACT

Background Progressive multifocal leukoencephalopathy affects about 4 percent of patients with the acquired immunodeficiency syndrome (AIDS), and survival after the diagnosis of leukoencephalopathy averages only about three months. There have been anecdotal reports of improvement but no controlled trials of therapy with antiretroviral treatment plus intravenous or intrathecal cytarabine.

Methods In this multicenter trial, 57 patients with human immunodeficiency virus (HIV) infection and biopsy-confirmed progressive multifocal leukoencephalopathy were randomly assigned to receive one of three treatments: antiretroviral therapy alone, antiretroviral therapy plus intravenous cytarabine, or antiretroviral therapy plus intrathecal cytarabine. After a lead-in period of 1 to 2 weeks, active treatment was given for 24 weeks. For most patients, antiretroviral therapy consisted of zidovudine plus either didanosine or stavudine.

Results At the time of the last analysis, 14 patients in each treatment group had died, and there were no significant differences in survival among the three groups ($P = 0.85$ by the log-rank test). The median survival times (11, 8, and 15 weeks) were similar to those in previous studies. Only seven patients completed the 24 weeks of treatment. Anemia and thrombocytopenia were more frequent in patients who received antiretroviral therapy in combination with intravenous cytarabine than in the other groups.

Conclusions Cytarabine administered either intravenously or intrathecally does not improve the prognosis of HIV-infected patients with progressive multifocal leukoencephalopathy who are treated with the antiretroviral agents we used, nor does high-dose antiretroviral therapy alone appear to improve survival over that reported in untreated patients. (N Engl J Med 1998;338:1345-51.)

PROGRESSIVE multifocal leukoencephalopathy[1] results from infection with a human DNA papovavirus, designated JC virus,[2] and occurs in conditions associated with deficient cell-mediated immunity.[3] It is estimated to affect up to 4 percent of all patients with the acquired immunodeficiency syndrome (AIDS).[4] No effective therapy has been established.

Suspicion of progressive multifocal leukoencephalopathy is aroused by characteristic clinical and neuroradiologic abnormalities in an immunocompromised host. Other disorders, including cytomegalovirus infection, central nervous system lymphoma, and encephalitis caused by infection with the human immunodeficiency virus (HIV), may mimic progressive multifocal leukoencephalopathy, and definitive diagnosis requires the evaluation of tissue. Stereotactic brain biopsy has proved to be effective for this purpose.[5,6] Recent studies indicate that the presence of JC virus in cerebrospinal fluid, as identified by the polymerase chain reaction (PCR), has high specificity for the diagnosis of active disease.[7,8] Average survival after diagnosis in HIV-infected patients ranges from approximately 2.5 months[9] to 4 months.[4] Remission, prolonged survival, and even spontaneous recovery may occur, however.[10-12] Berger et al. have estimated that in approximately 7 percent of patients, progressive multifocal leukoencephalopathy follows a more benign course, with survival of more than one year.[13]

Treatment with prednisone, acyclovir, vidarabine (given either intravenously or intrathecally), HLA-matched platelets, and interferon alfa have not resulted in consistent improvement in patients with progressive multifocal leukoencephalopathy.[14-19] In patients with AIDS, both antiretroviral agents and cytarabine have been found to be efficacious in some small, uncontrolled studies but not in others. Such reports have led to the frequent use of cytarabine in patients with AIDS who have progressive multifocal

From the University of North Carolina at Chapel Hill School of Medicine, Chapel Hill (C.D.H.); Harvard School of Public Health, Boston (U.D., C.Y.); Mount Sinai School of Medicine, New York (D.S.); Washington University School of Medicine, St. Louis (D.C.); Yale University School of Medicine, New Haven, Conn. (P.E.W.); Northwestern University School of Medicine, Chicago (B.C.); the Departments of Neurology and Epidemiology, Johns Hopkins School of Medicine, Baltimore (J.M.); the University of California at San Francisco School of Medicine, San Francisco (H.H.); the National Institute of Neurological Disorders and Stroke, Bethesda, Md. (E.M.); Frontier Science and Technology Research Foundation, Amherst, N.Y. (L.M.); and Washington, D.C., General Hospital, Washington, D.C. (J.T.). Address reprint requests to Dr. Hall at the Department of Neurology, CB7025, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7025.

*Other participants in the study are listed in the Appendix.

leukoencephalopathy. Because cytarabine has severe side effects, including immune suppression, this unestablished therapy entails considerable risk.

AIDS Clinical Trials Group (ACTG) Study 243 was a multicenter study comparing antiretroviral medication alone with antiretroviral therapy plus cytarabine for the treatment of progressive multifocal leukoencephalopathy in HIV-infected subjects. The protocol ensured that the diagnosis of progressive multifocal leukoencephalopathy was based on tissue evaluation.

METHODS

Study Design

This trial was a randomized, multicenter, open-label study, designed to enroll 90 patients of either sex. All subjects had HIV type 1 infection and clinical and radiologic findings indicative of progressive multifocal leukoencephalopathy. All subjects were required to have the diagnosis established within two months of study entry. Tissue obtained by stereotactic brain biopsy was evaluated both by standard neuropathological examination at the study center and by in situ hybridization for JC virus,[20] conducted at the National Institute of Neurological Disorders and Stroke. Subjects were eligible only if at least one of these tests confirmed the diagnosis. Cerebrospinal fluid was evaluated by PCR for the presence of JC virus in a number of subjects. Other criteria for inclusion were an age of 18 to 65 years, an absolute neutrophil count of 750 cells per cubic millimeter or higher, a platelet count of 50,000 per cubic millimeter or higher, serum concentrations of alanine aminotransferase, aspartate aminotransferase, or both that were less than five times the upper limit of normal, the ability to provide informed consent or the assignment of a durable power of attorney, and, in the case of women, a negative serum pregnancy test and use of adequate contraception throughout the study.

Exclusion criteria included the administration within the past 14 days of interferon, ganciclovir, foscarnet, antiretroviral therapy other than zidovudine, didanosine, or zalcitabine, or experimental drugs for the treatment of progressive multifocal leukoencephalopathy; systemic chemotherapy for cancer; prior treatment with cytarabine; an active opportunistic infection; conditions precluding the placement of an Ommaya reservoir; intolerance of all the antiretroviral medications used in the study; allergy to or intolerance of filgrastim (granulocyte colony-stimulating factor); and other life-threatening complications likely to cause death within three months.

An ACTG neurologist conducted all neurologic evaluations. Optimal antiretroviral therapy was determined during a lead-in period of one to two weeks; the preferred therapy was 300 mg of zidovudine three times a day and 200 mg of didanosine (125 mg if the patient weighed less than 60 kg) twice a day. Subjects already receiving zalcitabine and those with a history of intolerance of didanosine received 0.75 mg of zalcitabine three times a day in addition to zidovudine. Subjects who were unable to tolerate either didanosine or zalcitabine could enter the study and receive zidovudine alone. Before enrollment was completed, new antiretroviral agents were approved by the Food and Drug Administration and were permitted in the study.

After the lead-in period, subjects were randomly assigned to one of three treatments, each of which was given for 24 weeks. Group 1 continued to receive the antiretroviral regimen established during the lead-in period, with dose adjustments to reduce or eliminate toxic effects. Group 2 continued to receive the established antiretroviral regimen and also received 4 mg of cytarabine per kilogram of body weight daily for 5 days by intravenous infusion, followed by a 16-day period when antiretroviral therapy alone was given. This 21-day cycle was repeated throughout the study. Group 3 received antiretroviral therapy plus 50 mg of cytarabine, administered intrathecally with an Ommaya reservoir, once a week for four weeks, then once every two weeks for eight weeks, then once every four weeks for the remainder of the study. Filgrastim was administered to all subjects in group 2 after each five-day cycle of cytarabine; it was administered to patients in the other groups when required to counteract neutropenia.

An external performance and safety monitoring board closely monitored the study. A first interim review was conducted at 18 months; on the basis of the interim results, the board recommended that the study continue. A second interim review was conducted when 50 percent of the expected events had occurred. After the second review, the board concluded that no treatment was likely to show a survival benefit, even if the study were continued to completion. On the basis of that recommendation, the study was terminated at 24 months.

Statistical Analysis

An intention-to-treat analysis was performed that included all eligible subjects randomly assigned to the three treatment groups. Kruskal–Wallis and Fisher's exact tests were used to compare continuous and discrete measures, respectively, among the treatment groups. Differences in the length of time to the occurrence of a first adverse effect due to drug toxicity and the length of time to death were tested by the log-rank test. The Kaplan–Meier method was used to estimate survival in the three groups.

Analyses were based on stochastic curtailment methods for the primary end point (survival). These methods were used to estimate the conditional power of the study if it were to be completed, given the observed data up to each interim analysis. These estimates were derived by simulation and by analytic techniques, with use of the normal approximation. Reported P values are two-sided.

RESULTS

Subjects

The study was open for enrollment from April 1994 to August 1996. Sixty-four patients were enrolled at 13 ACTG sites. The study was approved by the institutional review board at each site, and all subjects provided written informed consent. Data on 62 patients enrolled before May 1996 were available during the second (final) interim analysis. Three subjects were lost to follow-up or withdrew during the lead-in period and were therefore not randomly assigned to a treatment group. Brain biopsies were positive in 49 patients by both methods (Table 1); 3 subjects were positive on in situ hybridization but not on microscopical examination; 5 were positive on microscopical analysis but not on in situ hybridization. Two additional patients were considered ineligible, since neither the neuropathological nor the in situ evaluation confirmed the diagnosis. The reported results are thus based on 57 patients who could be evaluated. One of these did not receive any study medication.

Most of the patients were men (82 percent), and 65 percent were non-Hispanic whites. As Table 2 shows, their median age was 38 years (range, 26 to 54), and they had a median of 13 years of education (range, 9 to 18). The overall median Karnofsky score was 60 (range, 30 to 90). The median CD4+ count (53; range, 0 to 420) reflects the advanced

TABLE 1. BASE-LINE BIOPSY RESULTS IN PATIENTS WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY, ACCORDING TO TREATMENT GROUP.*

GROUP AND RESULT	NO. (%)
Intravenous-cytarabine group (n=20)	
Both positive	18 (90)
Only neuropathological examination positive	2 (10)
Intrathecal-cytarabine group (n=19)	
Both positive	16 (84)
Only neuropathological examination positive	2 (11)
Only in situ hybridization positive	1 (5)
Antiretroviral-therapy-only group (n=18)	
Both positive	15 (83)
Only neuropathological examination positive	1 (6)
Only in situ hybridization positive	2 (11)

*The diagnosis could be confirmed on brain biopsy by positive neuropathological examination, positive in situ hybridization, or both.

stage of HIV disease in this cohort. Twenty patients were randomly assigned to the intravenous-cytarabine group (group 2), 19 to the intrathecal-cytarabine group (group 3), and 18 to the antiretroviral-therapy-only group (group 1). After randomization, the intravenous-cytarabine group was found to contain only male subjects ($P=0.015$ for the comparison among the three groups, and $P=0.71$ for the comparison between all patients who received cytarabine and those who did not). With the exception of sex, there were no significant differences in baseline characteristics among the treatment groups.

At base line, the following abnormalities and symptoms were present: diminished cognitive function in 79 percent of the patients, motor-coordination defects in 77 percent, sensory loss in 47 percent, visual loss in 39 percent, headache in 28 percent, and seizures in 16 percent. No significant differences were detected when we compared the three treatment groups (or when we compared the two groups receiving cytarabine with that receiving only antiretroviral therapy) with respect to neurologic history and signs, symptoms, or abnormalities in blood chemistry at base line. Subjects receiving only antiretroviral therapy had, on average, significantly lower absolute neutrophil counts than the other two groups ($P=0.075$ and $P=0.023$ for the three-way and two-way comparisons, respectively), as well as lower white-cell counts ($P=0.032$ and $P=0.083$, respectively). The treatment groups did not differ significantly with respect to the frequency of any other hematologic abnormality at base line.

The majority of subjects (44, or 77 percent) had received zidovudine before entering the study. Didanosine alone or in combination had been taken by 21 patients (37 percent), stavudine by 14 patients (25 percent), and zalcitabine by 8 patients (14 percent). A history of treatment with saquinavir in combination with other antiretroviral agents was reported by three patients (5 percent; one in the intravenous-cytarabine group and two in the intrathecal-cytarabine group), and a history of ritonavir treatment by one patient in the intrathecal-cytarabine group. Seven patients did not report any prior use of antiretroviral agents.

Follow-up

All 57 patients, including those who successfully completed 24 weeks of therapy, were followed while receiving the assigned drug until the end of the study or until they died. The median follow-up was 8.7 weeks and did not differ significantly among the three treatment groups ($P=0.78$ and $P=0.66$ by the log-rank test for the three-way and two-way comparisons, respectively).

Seven patients completed the 24-week treatment. Three (one in each group) who were receiving active therapy at the time the study was terminated discontinued treatment at that time. Table 3 lists the reasons for permanent discontinuation of treatment.

TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC	ALL PATIENTS (N=57)	INTRAVENOUS CYTARABINE (N=20)	INTRATHECAL CYTARABINE (N=19)	ANTIRETROVIRAL THERAPY ONLY (N=18)	P VALUE*
	median (range)				
Age (yr)	38 (26–54)	37.5 (26–50)	38 (33–54)	39 (28–53)	0.68
Education (yr)	13 (9–18)	14 (11–17)	12 (9–18)	13 (12–18)	0.20
Karnofsky score†	60 (30–90)	60 (30–80)	60 (30–90)	60 (30–90)	0.95
CD4+ count (cells/mm^3)	53 (0–420)	106 (0–220)	29 (0–420)	53 (0–211)	0.09

*P values were calculated with the Kruskal–Wallis nonparametric test.

†The Karnofsky performance score, a measure of functional ability, ranges from 0 to 100, with higher scores indicating better performance.

Twenty-two patients (39 percent) died during the study. One patient in the intrathecal-cytarabine group and one in the intravenous-cytarabine group discontinued treatment because of thrombocytopenia, as required by the protocol. Treatment was never dispensed to one patient in the antiretroviral-therapy-only group. Fourteen patients discontinued treatment at their own request, four at the request of the investigators, five because of drug-induced toxicity, and one at the start of other experimental treatment. The majority of the patients who discontinued treatment at their own or an investigator's request had been randomly assigned to receive intrathecal cytarabine (11 patients). The median length of treatment was longer for the antiretroviral-therapy-only group (8.9 weeks, vs. 6.4 weeks for the two cytarabine groups combined), but the difference was not significant ($P = 0.56$ and $P = 0.29$, respectively, by the log-rank test).

The median time to the first dose modification in the group receiving only antiretroviral therapy was more than double that in the two groups receiving cytarabine ($P = 0.03$ and $P = 0.01$ for the three-way and two-way comparisons, respectively, by the log-rank test). Thirteen of the 57 patients died while receiving the full dose of antiretroviral therapy and cytarabine (23 percent), and only 2, who were receiving antiretroviral therapy alone, completed treatment without any dose modification (4 percent). The chief reason for dose modification was a decision by the clinician or the patient (28 percent); this was particularly common in the intrathecal-cytarabine group (47 percent). The second-most-common reason overall (19 percent), and the commonest reason in the intravenous-cytarabine group (37 percent), was hematologic toxicity.

As antiretroviral medication, 29 patients (51 percent) received zidovudine combined with didanosine, 7 (12 percent) received zidovudine plus zalcitabine, and 7 (12 percent) received zidovudine alone. In addition to this therapy, 15 patients received stavudine, 5 lamivudine, 5 saquinavir, and 1 ritonavir. Saquinavir was given in combination with zidovudine and lamivudine to three patients and in combination with stavudine and lamivudine to one patient. Ritonavir was used in combination with zidovudine in one patient. Five subjects received other drug combinations containing zidovudine. Two patients received didanosine alone, and two zalcitabine alone. Compliance with antiretroviral therapy was assessed every 4 weeks and was consistently rated as good (more than 80 percent of medication taken) for the majority of the patients (90 percent) throughout the 24-week protocol.

Safety

The standardized ACTG scale for grading toxicity assigns a value from 0 to 5 to clinical and laboratory abnormalities, according to their severity. Twenty-three patients had drug-induced laboratory abnormalities rated grade 3 or higher. A larger number of patients in the intravenous-cytarabine group (11 of 20 patients [55 percent]) than in the other groups had laboratory evidence of drug toxicity, but the differences were not significant ($P = 0.22$ and $P = 0.81$ for the three-way and two-way comparisons, respectively, by the log-rank test).

No significant difference was detected among the groups with respect to blood chemical abnormalities (three patients in the antiretroviral-therapy-only group had such toxic effects, as did two in the intravenous-cytarabine group and one in the intrathecal-cytarabine group). Nineteen patients had evidence of hematologic toxicity rated grade 3 or higher during

TABLE 3. REASONS FOR DISCONTINUATION OF THE STUDY DRUGS, ACCORDING TO TREATMENT GROUP.

REASON	ALL PATIENTS (N=56)*	INTRAVENOUS CYTARABINE (N=20)	INTRATHECAL CYTARABINE (N=19)	ANTIRETROVIRAL THERAPY ONLY (N=17)*
	number (percent)			
Death	22 (39)	11 (55)	4 (21)	7 (41)
Patient's request	14 (25)	3 (15)	8 (42)	3 (18)
Completion of therapy†	10 (18)	3 (15)	3 (16)	4 (24)
Investigator's request	4 (7)	0	3 (16)	1 (6)
Drug toxicity	5 (9)	3 (15)	1 (5)	1 (6)
Experimental medication	1 (2)	0	0	1 (6)

*Fifty-seven eligible patients were randomly assigned to treatment, of whom one (in the antiretroviral-therapy-only group) never received the study medication. Percentages have been calculated with the number receiving treatment as the denominator.

†Of the 10 patients who completed treatment, 3 (1 in each study group) did so at the time of study termination.

the 24-week treatment period; the majority (10 patients) were in the intravenous-cytarabine group (50 percent of that group had such effects) (Table 4). Toxic effects (grade 3 or higher) on hemoglobin and platelet counts were more common and occurred earlier in the intravenous-cytarabine group than in the other two groups ($P = 0.05$ and $P = 0.01$, respectively, for the three-way comparisons and $P = 0.22$ and $P = 0.01$, respectively, for the two-way comparisons, by the log-rank test). No statistically significant difference was detected in effects on the absolute neutrophil counts. Hematologic toxicity was the primary reason for dose modification in the intravenous-cytarabine group, but only one patient permanently discontinued treatment for this reason. Thus, the time to the first dose modification differed significantly among groups, whereas the time to permanent discontinuation of treatment did not.

Twenty patients had signs or symptoms of toxicity rated grade 3 or higher during follow-up (nine, seven, and four in the intravenous-cytarabine, intrathecal-cytarabine, and antiretroviral-therapy-only groups, respectively). No significant differences were detected among the treatment groups.

Survival

Forty-two patients had died by the time the last analysis was performed (14 in each treatment group). Thirty-seven (88 percent) died of progressive multifocal leukoencephalopathy, two of progressive HIV disease, one of *Pneumocystis carinii* pneumonia, one of sepsis, and one of an unknown cause. Figure 1 shows the Kaplan–Meier survival curves for each of the three treatment groups; no significant difference among the groups was detected ($P = 0.85$ by the log-rank test). The intravenous-cytarabine group had the lowest median survival (7.6 weeks), but there were also four long-term survivors in this group who were still alive beyond week 60; however, two of the long-term survivors discontinued treatment early (during the first and seventh weeks of the study). No significant difference was found when we compared the antiretroviral-therapy-only group with the two cytarabine groups combined ($P = 0.85$ by the log-rank test).

At the time of the last analysis in July 1996, the performance and safety monitoring board had 59 percent of the information that would have been available if the study had continued to the originally intended end point (42 of the 71 deaths predicted by the completion of the trial had occurred). Conditional power, a measure of the chance of detecting a significant increase in the survival rate under different alternative assumptions, given the observed data patterns up to the time of the analysis, was calculated both by simulation and analytically (stochastic curtailment methods). The two alternatives considered in calculating the conditional power of the study were the continuation of the observed trend for the rest of the study and a doubling of survival among the remaining patients due to the effect of cytarabine. The conditional-power estimates, calculated analytically, were 0.4 percent when the three groups were compared and 15 percent when the cytarabine groups were combined (simulated values, 0.2 percent and 20 percent, respectively). Thus, there was no more than a 20 percent chance of rejecting the null hypothesis that there was no difference in survival among the treatments even if all future data supported the alternative hypothesis that cytarabine increases survival. The board concluded at that point that the study should be discontinued

TABLE 4. HEMATOLOGIC TOXIC EFFECTS RATED GRADE 3 OR HIGHER.

EFFECT	ALL PATIENTS (N = 56)*	INTRAVENOUS CYTARABINE (N = 20)	INTRATHECAL CYTARABINE (N = 19)	ANTIRETROVIRAL THERAPY ONLY (N = 17)*	P VALUE†	
					THREE-WAY	TWO-WAY
	number (percent)					
Hemoglobin, ≤6.5 g/dl	3 (5)	3 (15)	0	0	0.05	0.22
Absolute neutrophil count, ≤749/mm³	12 (21)	4 (20)	3 (16)	5 (29)	0.68	0.41
Platelet count, ≤49,999/mm³	11 (20)	8 (40)	3 (16)	0	0.01	0.01
Any of these effects	19 (34)	10 (50)	4 (21)	5 (29)	0.13	0.52

*Fifty-seven patients were randomly assigned to treatment, of whom one (in the antiretroviral-therapy-only group) never received the study medication. Percentages have been calculated with the number receiving treatment as the denominator.

†P values were calculated by the log-rank test, for the comparison of time to the occurrence of the first toxic effect.

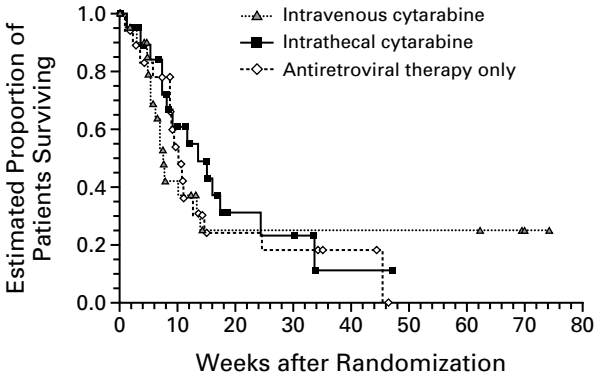

Figure 1. Kaplan–Meier Curves for Survival in the Three Treatment Groups.

The median survival was 8 weeks in the intravenous-cytarabine group (in which 14 of 20 patients died), 15 weeks in the intrathecal-cytarabine group (14 of 19 patients died), and 11 weeks in the antiretroviral-therapy-only group (14 of 18 patients died). P=0.85 by the log-rank test for the comparison among the groups.

and the results disseminated in order to spare patients from undergoing an intense, invasive, and ineffective therapy.

DISCUSSION

Most of the literature on the effect of antiretroviral therapy alone and in combination with intravenous or intrathecal cytarabine for the treatment of progressive multifocal leukoencephalopathy in patients with AIDS has been anecdotal and conflicting. Some investigators have reported improvement in patients with AIDS and suspected or biopsy-proved progressive multifocal leukoencephalopathy after the administration of zidovudine or other antiretroviral agents,[21-23] but not all investigators have had similar results.[24] There have also been reports of improvement in non–HIV-related progressive multifocal leukoencephalopathy when cytarabine has been given intravenously, intrathecally, or both,[25-27] and there are similar reports of improvement in patients with AIDS.[21,28-30] Some patients appeared to respond to intravenous cytarabine, others to intrathecal cytarabine, and some to a combination. On the other hand, Urtizberea et al. found no benefit of intravenous and intrathecal cytarabine.[31] Fong et al., in a prospective and retrospective study of 28 patients, found no benefit in the 9 who had been treated with cytarabine.[32] In addition, although cytarabine has an antiviral effect in cell culture,[33] a therapeutic effect in vivo has not been established.[34,35]

ACTG Study 243 was a prospective investigation of progressive multifocal leukoencephalopathy that was designed to address several important issues. To ensure that the approximately 7 percent of patients who appear to have a more benign course were not overrepresented, subjects were required to have progressive multifocal leukoencephalopathy diagnosed within two months of study entry. All diagnoses were confirmed in brain-biopsy specimens by either typical neuropathological findings or in situ hybridization for JC virus. The in situ hybridization was performed at a central site where the investigators had the requisite expertise (the laboratory of Dr. Major at the National Institute of Neurological Disorders and Stroke).

Enrollment of patients and prevention of withdrawals are difficult in clinical trials of rapidly progressive diseases with high fatality rates. Further difficulties associated with the current trial included the frequency of concomitant disabling HIV-related illnesses, the need for subjects to undergo brain biopsy, and the side effects of the prescribed medications, both the antiretroviral drugs and cytarabine. To make the evaluation of effects of medication more accurate, subjects likely to die from causes other than progressive multifocal leukoencephalopathy in less than three months were not enrolled, and most subjects did not have progressive multifocal leukoencephalopathy at a stage that was so advanced as to preclude a therapeutic effect if cytarabine had been effective.

We believe our negative results have direct relevance to clinical practice. Although there was no double-placebo group (i.e., no group that received neither antiretroviral drugs nor cytarabine), the median survival (1.75 to 3.5 months) was very close to that predicted from a review of the literature (2.5 to 4 months), indicating that antiretroviral therapy had no benefit. There were also no significant differences between the group treated with antiretroviral drugs alone and the groups that received intravenous or intrathecal cytarabine. This study was conducted before the advent of highly active antiretroviral therapy, which has been reported to be associated with regression of progressive multifocal leukoencephalopathy.[36,37] Our results provide useful comparative data for future studies incorporating highly active antiretroviral therapy, as well as agents more specifically directed against JC virus.

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APPENDIX

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