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Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-Interferon: an observational study

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A retrospective chart review was conducted to determine the effect of alpha-Interferon (alpha-IFN) on disease progresssion, symptom palliation, and survival in HIV-associated Progressive Multifocal Leukoencephalopathy (PML). *Methods:* Subjects were HIV seropositive patients diagnosed with PML at the Johns Hopkins Hospital between 1985 and July of 1986. Diagnostic criteria for PML included both clinical symptomatology and histologic or radiographic confirmation. All patients with concomitant CNS infections were excluded. Patients receiving a mininum treatment of 3 weeks of 3 million units of alpha-IFN daily were compared to untreated historical controls. From 104 PML cases reviewed, 77 met the defined criteria for PML. Twenty-one patients had received open-label α-IFN treatment in a non-randomized manner for at least 3 weeks, and 32 met criteria for inclusion in the untreated group as historical controls. Deceased treated patients were comparable to deceased untreated patients with respect to age, gender, race, HIV risk factors, AIDS-defining illnesses, and CD4+ counts. CD4+ counts and use of anti-retroviral medications within 6 months of PML onset were higher among those who were living at the time of the study. *Results:* Among deceased patients, median survival of treated patients was 127.5 days longer than that of untreated patients (Chi-square=4.21, P=0.04). When living and deceased treated patients were combined, the median survival was 325 days (range 35–1634) *versus* 121 days (range 46–176) in untreated patients (Chi-square=13.47, $P < 0.001$). When survival times in untreated patients were left-censored to account for possible survivorship bias in treated patients, survival in treated patients remained significantly prolonged (325 days *versus* 175.5 days, Chi-square=4.65, P=0.03). In addition, use of alpha-IFN was associated with a significant delay in the onset of memory loss (Chi-square=8.59, $P < 0.01$). Seven alpha-IFN treated patients showed sustained remissions of several months to over a year, with documented improvements in mental status, aphasia, dysarthria, dysphagia, paresis, and dyscoordination. Moreover, four IFN-treated patients had evidence of MRI lesion regression, although this was not always correlated with clinical remission. Four of 32 untreated patients also reported transient symptomatic improvements. *Conclusion:* This open-label study suggests that α-IFN may delay progression, palliate symptoms, and significantly prolong survival in HIV-associated PML, and we therefore suggest that a controlled clinical trial is warranted.

Keywords: HIV; PML; alpha-interferon; magnetic resonance imaging

Introduction

Progressive multifocal leukoencephalopathy (PML) is an aggressive demyelinating disease that rapidly affects multiple functional capacities of the CNS. Classically, its clinical picture involves vision loss, extremity weakness, and mental status changes, commonly presenting as hemiparesis, homonymous hemianopsia, and confusion (Berger *et al*, 1987; Berger and Levy, 1997; Brooks and Walker, 1984). Cranial nerve deficits, cerebellar signs, and other neurologic symptoms tend to develop with disease progression.

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The agent in PML is almost always the JC virus, a member of the polyoma genus and the papovavirus family (ZuRhein and Chou, 1965). In human hosts, it can access the CNS, infect oligodendrocytes, and disrupt production of myelin proteins (Trapp *et al*, 1988). Histologically, this results in multifocal demyelinating plaques largely involving the subcortical U-fibers, with sparing of the cortical ribbon and deep gray matter. Lesions frequently originate in the parietal-occipital area, but can occur throughout the deep white matter, with eventual confluent and widespread demyelination.

The JC virus is ubiquitious, infecting 50% of children by the ages of 6–10 years, and 80–90% of adults by mid-life (Walker and Padgett, 1993). Following primary infection and viremia, JCV becomes latent in the kidney epithelium. In immunocompromised hosts, viral reactivation can result in CNS seeding via hematogenous spread through lymphocytes (Houff *et al*, 1988). Currently, AIDS has become the most common risk factor for PML with a prevalence of 4–6% and rising incidence rates (Gillespie *et al*, 1991; Major and Ault, 1995).

Average survival in non-AIDS patients is 9 months, and survival in AIDs patients, only 4 months (Berger and Concha, 1995). Moreover, although cases of spontaneous remission and prolonged survival exist, proposed treatment regimens have been largely unsuccessful (Major *et al*, 1992). Prior studies with adenosine arabinase and iododeoxyuridine had no beneficial effect, and results from a large-scale double-blind randomized clinical trial suggest no survival benefit from either intravenous or intrathecal ara-C (C Hall, personal communication).

Alpha interferon (α-IFN) was proposed as a treatment for JCV by Dr Joseph Berger because it successfully treats anogenital warts caused by another virus, Human Papilloma Virus (Gall, 1995). In two case reports, use of alpha-IFN significantly improved PML symptoms (Steiger *et al*, 1993; Colosimo *et al*, 1992). Additionally, Berger *et al* (1992) report increased survival in 2 of 17 patients treated with alpha-IFN-2a, although no improvements in neurological symptoms were seen. A small series of four patients with HIV-associated PML were treated with open label alpha interferon 5 to 10 million units daily for 4 to 12 weeks. None of the patients showed any clinical response and the mean survival was 14 weeks (Counihan *et al*, 1996).

Interferons are proteins released from virally infected cells to interfere with viral superinfection or spread to non-infected host cells. They augment Natural Killer and Killer cell activity, exert antiproliferative effects, breakdown viral RNA (Gutterman, 1994) and block viral translation. Alpha Interferon currently exists in two recombinant forms and a human-derived lymphoblastoid mixture. Recombinant IFNα-2a (Roche) and IFNα-2b (Schering) differ by two amino acids and are therapeutically similar, although the latter is more frequently used for HPV infections (Gall, 1995). We performed an observational study to evaluate survival benefit and symptom palliation in HIV+ PML patients treated with recombinant IFNα, mainly the 2b subtype.

Study design

Chart review was conducted in a retrospective study of all HIV seropositive adult patients diagnosed with PML at the Johns Hopkins University Neurology Department between 1985 and July of 1986. This was an open-label observational study, with no random treatment assignments. Decisions to initiate alpha-interferon were made jointly by patient and treating neurologist after review of therapeutic options. Patient charts were screened for prior use of alpha-Interferon, and comparison of therapeutic benefit was made using historical controls. Patient information was obtained from clinic charts and databases maintained by the HIV Neurology Program and the HIV Outpatient Clinic.

Analysis

Comparisons were made between groups A, B and C concerning demographic information, prior AIDS defining illnesses, survival from symptom onset, CD4+ count, anti-retroviral medications, and length and dose of alpha-IFN treatment. Kaplan-Meier survival curves were compared between group A (deceased, untreated) and patients treated with alpha-IFN regardless of vital status (groups B and C combined). Kaplan-Meier curves were subsequently adjusted to account for any survival bias in treated patients by left-censoring untreated patients according to the median time to treatment of the alpha-IFN group. Living patients from group C were right-censored according to an arbitrary end-date, July 19, 1996. Groups A and B were further examined for secondary outcomes regarding the development of new neurologic deficits. Finally, patients who received alpha-IFN treatment were stratified according to presence or absence of clinical improvement on neurological exam (responders and non-responders, respectively). These two groups were compared with regard to demographic information, calendar year of disease onset, CD4+ count, anti-retroviral medications, and time from symptom onset to treatment initiation.

All statistical analyses were conducted using SAS PC version 6.0 software (SAS Institute, Cary, NC). Continuous variables were examined using the Student's two-tailed *t*-test and linear regression methods, and dichotomous variables were exam-

ined using Log-Rank methods. Survival curves were compared using the Log-Rank method.

Results

Descriptive information

Table 1 includes descriptive information for groups A–C. A higher percentage of alpha-IFN treated patients had undergone biopsy with subsequent histological confirmation of PML. No significant differences were found between groups A–C with regard to age, gender, race, and HIV risk factor(s). CD4+ counts within 6 months of symptom onset were not significantly different between group A (70.4 cells/mm^3, s.d.=64.5) and group B (39.5 cells/mm^3, s.d.=35.9). However, the mean CD4+ count in group C, (excluding one outlier, CD4+=525) (95.0 cells/mm^3, s.d.=65.7) was significantly higher than group B (t=2.22, $P<0.05$). A higher percentage of group C patients were on protease inhibitors and nucleoside analogs *versus* groups A and B. Group C patients also developed PML in more recent years (1992–1996) *versus* group A (1987–1996) and group B (1989–1995).

Table 1 Descriptive information for groups stratified by alpha-IFN treatment and vital status at the time of review. No statistically significant difference was found among the groups in terms of gender, race, HIV risk factor, or age at onset. Year of PML onset was more recent for the living, treated group. No statistical difference in mean CD4+ count was found between deceased treated and untreated patients. A significantly higher mean CD4+ count was found for the living, treated group in comparison to the deceased, treated group (t=2.22, $P<0.05$). A greater percentage of deceased, treated patients had histologic confirmation of PML in comparison to deceased, untreated patients.

	Untreated (n=*32*)	*Treated: deceased* (n=*14*)	*Treated: living* (n=*7*)
Age at onset	39.9 years s.d. 6.49	35.7 years s.d. 7.02	41.5 years s.d. 8.30
Gender			
M	31 (96.9%)	12 (85.7%)	7 (100%)
F	1 (3.1%)	2 (14.3%)	0
Race			
African Am.	14 (43.8%)	5 (35.7%)	4 (57.1%)
Caucasian	17 (53.1%)	9 (64.3%)	3 (42.8%)
Hispanic	1 (3.1%)	0	0
HIV risk factors			
Homo/Bisex	16 (50.0%)	7 (50.0%)	4 (57.1%)
IVDU	6 (18.8%)	1 (7.1%)	3 (42.9%)
Homo/IVDU	0	1 (7.1%)	0
Transfusion	0	1 (7.1%)	0
Heterosex	1 (3.1%)	2 (14.3%)	0
Unknown	9 (28.1%)	2 (14.3%)	0
CD4+ Count*	70.4 s.d. 64.5	39.5 s.d. 35.9	95.0 s.d. 65.8
Average year of onset	1992	1993	1994
Histologic confirmation			
Autopsy	7 (21.9%)	6 (42.9%)	0
Biopsy	5 (15.6%)	4 (28.6%)	0
Total	11 (34.4%)	7 (50.0%)	0

*Within 6 months of PML onset. CD4+ counts were not available for all patients. n values for CD4+ counts are 22, 11, and 5 for untreated, deceased treated, and living treated groups, respectively.

Survival outcome

Survival from onset of PML symptoms was compared between treated and untreated deceased patients. Median survival of treated patients (group B) was 128 days longer than that of untreated patients (group A) (Chi-square=4.21, P=0.04). Median survival was 121 days (range 46–716 days) for group A and 248.5 days (range 87–754 days) for group B. Most patients died fromm neurological progression. Dosage effect could not be assessed because most patients empirically received 3 MU α-IFN SQ qd without escalation of treatment dose. In addition, survival was determined for group C (living, treated) using 7-19-96 as the censor date. Median survival was 310 days (range 46–716 days) for the seven patients.

Survival curves comparing group A (deceased, untreated) to all patients who had received at least 3 weeks of α-IFN (groups B and C combined) are shown in Figure 1. Treated patients (groups B and C) had a significantly longer median survival time (325 days) than untreated patients (group A) (121 days) (Chi-square=13.47, $P<0.001$). Median survival was right-censored to account for currently living patients. No significant relationship was found between survival and treatment duration or how promptly α-IFN was initiated after symptom onset. When the curves were adjusted for the time between symptom onset and initiation of treatment (to minimize survivorship bias), differences in survival still remained significant (325 days *versus* 175.5 days, Chi-square=4.65, P=0.03).

Symptomatic progression

All patients were examined by a neurologist on multiple occasions. Judgment of progression and consistency of exam was aided by the fact that 83.1% of patients were examined by the same neurologist (JCM). We also compared symptomatic progression in groups A and B as a secondary endpoint using serial neurological evaluations. Group C had higher CD4 counts and a larger percentage were treated with newer anti-retrovirals which would make comparisons difficult to interpret. A total of 24 symptoms were evaluated in areas of mental status, vision, speech, strength, and ambulation. We assessed whether alpha-IFN treatment might have delayed the evolution of certain neurological deficits. The mean onset of 20 of 24 symptoms was delayed in the treated *versus*

untreated groups, with a statistically signficant delay noted for onset of memory loss (Chi-square=8.59, $P<0.01$) (Figure 2).

Clinical improvement: responders and non-responders

In addition to survival benefit, clinical improvements were assessed. Seven of the 21 patients (33%) who received alpha-IFN showed striking clinical improvement (Table 2) compared to four of 32 untreated patients who mostly showed transient benefit. Lag in initiating treatment, length of treatment until clinical improvement, and CD4+ counts are also listed in Table 2.

Patients who showed clinical improvement on alpha-IFN (Responders) did not differ from those who did not (Non-Responders) with regard to age, gender, race, HIV risk factor(s), year of disease onset, time from symptom onset to treatment initiation, or treatment duration (data not shown). Furthermore, no significant difference in CD4+ count or use of protease inhibitors was found. A significant difference was detected in survival with responders having a median survival of 753 days versus 182 days for non-responders (Chi-square=15.74, $P<0.001$).

Interestingly, four (12.5%) of 32 untreated patients had evidence of improvement. One reported remission of longstanding diplopia. Three presented with transient hemiparesis which was accompanied by mild dysarthria in two patients. Nevertheless, all symptoms resolved within 5 days of initial symptom presentation only to recur shortly thereafter.

Only two of the seven responders showed concomitant improvement on MRI as evidenced by decreasing size of white matter lesions (Figure 3).

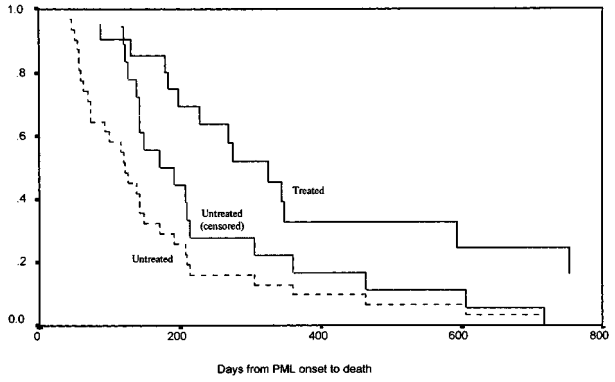

Figure 1 Survival curves for patient groups stratified by Interferon-Alpha-2b treatment. Survival days for treated patients includes all patients who received Interferon-alpha-2b regardless of vital status (group B, (treated, deceased) and group C (treated, living) combined). Median time to treatment was 122 days. Survival in group A (untreated) was presented in two ways: (1) simple days survival after onset of symptoms (dashed line) and (2) right-censored at 122 days to adjust for treatment lag (and survivorship bias) by excluding patients who did not survive to reach the median time of initiation of a-IFN among the treated patients (solid line). Survival (in days) from onset of PML in plotted against percentage of each group still living. Survival of treated patients is significantly prolonged versus survival of untreated patients (Chi-square=13.47, $P<0.001$) and of right-censored untreated patients (Chi-square=4.65, $P<0.03$).

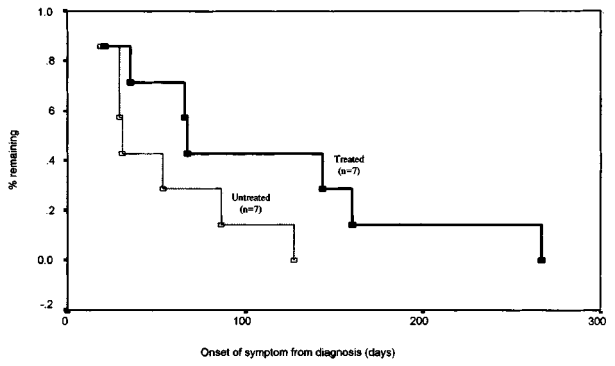

Figure 2 Alpha-Interferon effect on delaying memory loss. Graph reflecting all patients who subsequently developed memory loss. Patients were stratified by whether or not Interferon-alpha-2b was received as treatment. Development of memory loss is measured in days from initial PML symptoms plotted against percentage of patients with memory still intact. Patients treated with alpha-IFN showed a significant delay in onset of memory loss (Chi-square=8.59, $P<0.01$).

Table 2 Treatment parameters for all patients who had clinical improvement following institution of alpha-IFN therapy. No improvements were noted in these patients prior to initiation of interferon. Days to clinical improvement are highly dependent on patient-scheduled visits with the neurologist and may not accurately represent initial date of improvement. Only patients 2 and 7 showed corresponding MRI improvement.

	Time to RX	*CD4+Ct within 6 mo PML onset*	*Days of TX until improvement*	*Improvement symptom/sign*
Patient 1	112 D	88	82 D	Comprehension
			40 D	RUE paresis, aphasia
Patient 2	127 D	90	60 D	Aphasia
			141 D	Off assistive device
			317 D	Central facial paresis
			386 D	RUE paresis
Patient 3	93 D	96	181 D	Mental status change
			517 D	Dyscoordination, dysarthria
Patient 4	99 D	23	113 D	Dyscoordination
			185 D	Ataxia, RUE paresis
Patient 5	112 D	113*	35 D	Central facial paresis Speech, writing
Patient 6	218 D	525	102 D	Dysphagia
Patient 7	74 D	170	51 D	Dysphagia, dysarthria, aphasia

*CD4 count subsequently increased to 525 with initiation of AZT, 3TC, and alpha-IFN. CD4+ count was 170 at alpha-IFN onset.

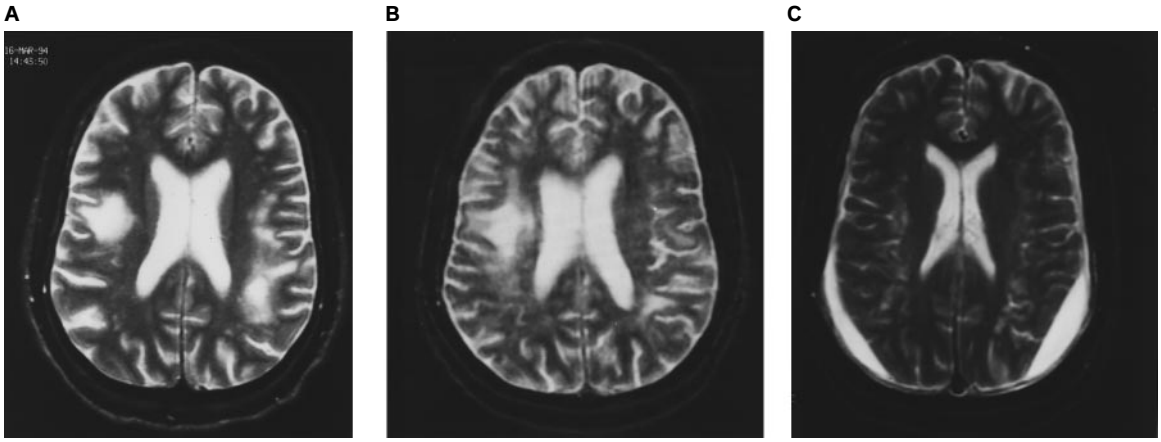

Figure 3 MRI scans from a patient achieving clinical and radiologic remission following alpha-Interferon-2b treatment. This patient presented with severe dysphagia and anarthria prior to treatment. In the year following treatment, the patient regained his ability to swallow. He also regained his ability to talk, first humming, then forming intelligible words, and eventually showing only slight dysarthria for a period of several months before subsequent decline. (**A**) T2-weighted MRI (3–94) demonstrates multiple white matter hyperintensities 1 month before treatment. (**B**) T2-weighted MRI (5–94) showing improvement of the parietal-occipetal lesion 37 days into treatment. (**C**) T2-weighted MRI (4–95) demonstrating continued improvement in white matter hyperintensities 11 months after a 51-day course of alpha-interferon treatment. Note bilateral subdural hematomas which developed after head trauma.

Two additional patients treated with alpha-IFN showed MRI improvement without clinical remission. In one patient, sustained radiologic improvement was seen over four MRIs spanning 1 year, followed by a period of stabilization over 7 months (two MRIs), followed by the subsequent appearance of new lesions (two MRIs). Only one untreated patient showed radiologic improvement (two MRIs over 2 months) followed by neurologic decline in the absence of clinical benefit.

Side effects

Over 80% tolerated subcutaneous alpha-IFN well. Of 21 patients who received it, only four developed side effects. These included leukopenia, pancytopenia, fatigue and depression at 9, 28, 40, and 90 days of treatment, respectively. All but fatigue resulted in cessation of drug treatment. It is unclear whether the leukopenia was due to alpha-IFN or concurrent AZT use given that the patient had a history of AZT-induced leukopenia. Both drugs were temporarily withdrawn and the leukopenia resolved.

Discussion

Our results suggest that treatment with recombinant IFN-alpha increases the survival of HIV+ PML patients compared to untreated historical controls. We further show that prolonged treatment with alpha-IFN may delay the onset of certain neurological symptoms in PML, and is associated with clinical remission in a higher proportion of patients than is typically seen in HIV-associated PML.

Deceased patients from untreated (group A) and treated (group B) alpha-IFN groups were comparable for gender, race, HIV risk factors, age, and year of symptom onset. No significant differences in CD4+ count or anti-retroviral usage was found between treated and untreated patients. Median survival of deceased treated patients (group B) was 127.5 days longer than that of deceased untreated patients (group A) (P=0.04). Living treated patients (group C) showed the most survival benefit at 2.5 times the untreated median survival. However, group C patients were almost the most recently diagnosed, and may have had access to newer anti-retroviral agents, accounting for their higher baseline CD4+ counts and contributing to improved survival. Several investigators have reported symptom palliation in patients with PML with highly active antiretroviral therapies (Henry *et al*, 1997; Elliot *et al*, 1996; Albrecht *et al*, 1997). When all treated patients, both living and deceased, were combined and compared to untreated patients, a survival gain of 204 days was found ($P<0.001$). Glesby and Hoover (1996) recently published a paper on survivorship bias whereby simply living long enough to be placed on a treatment regimen makes that treatment appear beneficial.

In accordance with prior studies (Berger and Concha, 1995), most of our patients initially presented with visual impairment, limb paresis, or confusion. Speech abnormalities and memory loss were less common initially, and presentations of

abnormal gait and dyscoordination were relatively infrequent at disease onset. In deceased patients who had received alpha-IFN treatment (group B), onset of memory, speech, and walking difficulties were significantly delayed compared to deceased untreated patients (group A).

Clinical remissions have been documented in untreated patients with PML (Berger and Mucke, 1988). We were therefore interested in whether alpha-IFN reversed or attenuated already-existing symptoms. We found that alpha-IFN treatment was associated with clinical remission in 33% of treated patients, a higher proportion than the 10% remission rate reported by Berger and Levy (1997). Improvements were seen in mental status, aphasia, dysarthria, dysphagia, paresis, and dyscoordination. Moreover, benefits appeared to be sustained for several months to over a year. As expected, those responding to alpha-IFN also showed longer median survival times of 753 days compared to 182 days in non-responders ($P<0.0001$).

There were no significant differences between Responders and non-Responders in terms of antiretroviral usage or immune status. A higher percentage of the responders received antiretrovirals (7 of 7 *versus* 11 of 14), but an equal proportion were on protease inhibitors. It is unlikely that the slightly more frequent use of antiretrovirals explains the beneficial clinical responses seen in responders, however, we were not able to assess adherence and viral load measurements were not available. There were no differences in demographic information, year of diagnosis, or time from symptom onset to treatment initiation. We showed no difference between responders and non-responders with respect to survival time prior to α-IFN, thus suggesting that survivorship bias does not account for the observed improvements in survival.

Four untreated patients showed clinical improvement. However, in three of the four cases, improvements were brief fluctuations of symptoms. The fourth case of resolved diplopia remains unexplained and may represent a spontaneous remission (see later discussion).

MRI improvement was noted in only a few cases, and did not correlate well with clinical remisison. Why some radiological lesions improve and others do not is unknown. Nevertheless, these cases suggest that alpha-IFN may interrupt JCV infection in a way that allows remyelination to occur. Alternatively, the signal changes may reflect normalization of interstitial water content rather than remyelination.

Alpha-IFN is well-absorbed subcutaneously in both the 2a and 2b forms. Our patients mostly received the 2b subtype. A study of alpha-IFN-2b in healthy volunteers (Radwanski *et al*, 1987) showed a 5.5 h absorption half-life, maximum serum concentrations 8 h after SQ dosing, and renal catabolism with a 2.9 h elimination half-life. Interestingly, alpha-IFN has poor access to the CNS (Smith *et al*, 1985), and treatment effects may be due to effects on circulating lymphocytes which subsequently traffic into the CNS and establish an immune response.

Side effects were seen in four (19%) of 21 of our patients. These included leukopenia, pancytopenia, depression, and fatigue resulting in transient drug cessation in two, and permanent discontinuation in two others. The most common side effects of alpha-IFN reported in the literature are flu-like symptoms including fevers, chills, headache, and myalgia (Vial and Descotes, 1994). A study of alpha-IFN in 11 asymptomatic HIV seropositive patients (Lane *et al*, 1990) treated with 35 MU SQ qd showed that 100% developed flu-like symptoms; 73%, diarrhea; 55%, granulocytopenia; 45%, elevated liver function tests; and 27%, proteinuria and depression. Side effects decreased with time and were dose-dependent which may explain the lesser incidence among our patients. A prior study in cancer patients (Kurschel *et al*, 1991) treated with 4 MU of alpha-IFN-2b also showed pathological proteinuria in 20%. Therefore, avoidance of additional nephrotoxic agents is recommended. Increased incidence of thyroid and other autoimmune disorders has been reported (Ronnblom *et al*, 1991). None of these latter complications were seen in our study.

The limitations of the study included small sample size, observational design, lack of systematic dose escalation, and unblinded examinations that may have influenced detected clinical improvements. In addition, as a referral base, our hospital's patients may not be representative of the general PML population.

Additionally, our results may be confounded by the fact that a small percentage of untreated PML patients undergo spontaneous remissions and prolonged survival (Berger and Mucke, 1988). The cause of this has remained a mystery, but is usually assumed to reflect immunological improvement sufficient to suppress the JC virus. One speculative explanation relates to the antigenic cross-reactivity that exists between the JC and SV40 viruses. In an untoward chain of events, adenovirus and poliovirus vaccines administered in the US from 1954–1963 were contaminated with SV40 (Shah and Nathanson, 1976). Over 98 million Americans received these vaccines, 10–30% of which carried live SV40. Moderately high levels of antibody to SV40 persist for years in these individuals. It is possible that these antibodies in some way attenuate JCV and induce remission in PML.

Choice of alpha-IFN21 *versus* subtype 2b may be important in maximizing efficacy in treatment of

PML. Neutralizing antibodies to IFN-alpha-2a are generated more readily (20%) than neutralizing antibodies to IFN-alpha-2b (3–7%) (Spiegel *et al*, 1989; Dianzani *et al*, 1989). Alpha-IFN antibody titers were not available in our retrospective study, but may explain why some treated patients showed transient or negligible benefit in symptom palliation and survival.

Prior therapies directed against JCV reactivation in compromised hosts have been unsuccessful. AZT has been ineffective (Major *et al*, 1992) despite the hope it would suppress HIV viral replication and improve immune status. Ara-C had been considered more promising (Portegies *et al*, 1991; Britton, 1992), until the recent analysis of a large-scale randomized clinical trial suggested otherwise (Hall, 1997).

Alpha-IFN evinces both anti-viral and immune-enhancing activity. Moreover, it has proven efficacy against HPV, a virus closely related to JCV. Steiger *et al* (1993) reported dramatic improvement in a patient treated with alpha-IFN after prior failure with Ara-C. Our retrospective review of 21 treated and 32 untreated HIV seropositive PML patients suggests that IFN-alpha-2b not only significantly prolongs survival, but may delay disease progression and reverse existing symptoms in some patients. We believe that evaluation of alpha-IFN-2b within a randomized clinical trial is warranted.

Methods

Inclusion criteria consisted of HIV seropositivity, age >18, diagnosis of PML, and absence of confounding CNS opportunistic processes or cerebrovascular disease during diagnosis or subsequent follow up. Diagnosis of PML required (1) clinical diagnosis by a neurologist, (2) documented focal neurological findings on neurological exam, and either (3a) radiographic, or (3b) histological evidence as defined below. The onset of symptoms was estimated from the clinical documentation, and this date was used in subsequent analyses.

Radiographic criteria included focal white matter abnormalities with subcortical U-fiber involvement. All lesions spared gray matter structures, lacked mass effect, and were non-enhancing. Additionally, all were hyperintense on T2-weighted images, and hypointense on T1-weighted images.

Biopsy and autopsy reports were used to validate a diagnosis of PML. Brain tissue diagnoses required (1) demyelination, (2) hyperchromatic, enlarged oligodendroglial nuclei with basophilic nuclear inclusion bodies, and (3) enlarged lobulated bizarre-appearing astrocytes. Electron microscopy, SV40 immunostaining, and PCR for JCV were also acceptable methods to confirm PML and were frequently employed if histopathological features were ambiguous. Patients were excluded if biopsy or autopsy revealed any concurrent CNS infections such as toxoplasmosis, lymphoma, or neurosyphilis.

Medical records of 104 patients in the database were reviewed. Only 77 patients had definitive PML as defined by the above criteria. Of the 77, 23 patients were excluded for the following reasons: four had concomitant CNS infection (three with toxoplasmosis, one with cryptococcus), one died prematurely from biopsy complications, nine had received alternative therapy (ara-C) for PML, five had received <21 days of alpha-IFN, and four had unknown vital status. The remaining 53 patients were stratified into the following three groups: group A, deceased, no alpha-IFN treatment (n=32); group B, deceased, treated with alpha-IFN (n=14); group C, living, treated with alpha-IFN (n=7). The single living untreated patient was excluded from the analysis. Prior to reviewing the charts, a treatment trial was arbitrarily defined as $\geqslant 21$ consecutive days with a minimum alpha-IFN dosage of 3 million units (MU) SQ qd or 5 MU SQ three times a week. The majority of patients received alpha-IFN-2b (Schering) either directly from the JHH AIDS clinic, or through an on-site pharmacy.

Charts were screened for general descriptive information, other AIDS defining illnesses, confirmation of HIV seropositivity, CD4+ counts within 6 months of disease onset, date of symptom onset, concurrent retroviral medications, and any microbiologic or CSF results. Use of alpha-IFN was recorded by dose, treatment duration, compliance, and side effects. Available biopsy, autopsy, radiologic, and medical records were reviewed, and effort was made to obtain cause and date of death where appropriate. Neurological findings were logged by date of neurologist's exam with attention paid to gradations of dysfunction in vision, speech, strength, ambulation, and mental status. Occasionally, chart information was supplemented by records from hospice establishments, primary care physicians, and referring doctors.

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