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Clinical Trial Report

Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside

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This open label study determined the outcome of non-AIDS progressive multifocal leukoencephalopathy patients treated with a standard dose of intravenous cytosine arabinoside. Nineteen patients with PML proven by brain biopsy or spinal fluid polymerase chain reaction were treated with intravenous cytosine arabinoside 2 mg/kg per day for 5 days and followed for neurologic outcome by neurologic examination and MRI scanning. Seven of 19 PML patients treated with cytosine arabinoside intravenously improved neurologically. The range of follow-up for these patients was 2.0 to 4.5 years. All were left with neurologic deficits but were functionally improved, and 6 of 7 were able to independently carry out the activities of daily living. Twelve PML patients showed no evidence of response and died rapidly of their disease after treatment (range, 8 days to 6 months). All who survived their neurologic disease recovered from treatment-induced pancytopenia. Cytosine arabinoside given intravenously to non-AIDS PML patients in this small study was associated with a 36% chance of developing stabilization at 1 year. Treatment was associated with significant bone marrow toxicity. The improvement in MRI scan changes in those patients who responded took 6 weeks or longer. *Journal of NeuroVirology* (2001) **7,** 386–390.

Progressive multifocal leukoencephalopathy (PML) is currently without a satisfactory treatment. Although PML has been most commonly associated with AIDS since 1983 (Clifford *et al*, 1993), non-AIDS related PML continues to occur in patients with other forms of cell-mediated immune deficiency. One study looking at brain biopsy and autopsy cases noted 28 of 67 patients (42%) had non-AIDS related PML (Aksamit, 1993). Cytosine arabinoside (ARA-C, cytarabine) had anecdotally been reported to induce remission of this viral disease, but the dose and route of administration (intravenous, intrathecal, or both) of the drug has varied widely (Bauer *et al*, 1973; Marriott *et al*, 1975; Rockwell *et al*, 1976; Peters *et al*, 1980; Saxton *et al*, 1984; Schlitt *et al*, 1986; O'Riordan *et al*, 1990; Portegies *et al*, 1991; Lidman *et al*, 1991; Nicoli *et al*, 1992; Steiger *et al*, 1993). A recent controlled trial of ARA-C in AIDS-related PML patients has suggested it is ineffective in altering the course of disease (Hall *et al*, 1998). No single regimen of the ARA-C has been used in a series of non–AIDS-related PML patients to establish a response rate.

The natural history of non-AIDS PML is hard to establish with accuracy. The survival of patients is complicated by morbidity from underlying immunosuppressive illness and other coincident opportunistic infections. However, a large series of PML patients, which included only 3% AIDS-related PML, suggested 90% of PML patients die within 12 months of the onset of symptoms (Brooks and Walker, 1984).

There are anecdotal reports of spontaneous remission of PML both associated with (Berger and Mucke, 1988) and without AIDS (Price *et al*, 1983). Prolonged survival has sometimes been associated with the rare pathologic finding of prominent perivascular inflammatory reaction in the brain (Rockwell *et al*, 1976; Price *et al*, 1983; Kepes *et al*, 1975). There has been no large series to correlate duration of clinical symptoms, inflammatory pathologic findings at biopsy, and survival.

Between 1985 and 1998, 19 patients with PML not associated with AIDS were seen at the Mayo Clinic

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and diagnosed by brain biopsy or polymerase chain reaction (PCR) amplification of JC virus from spinal fluid. The patients were treated in a uniform manner with ARA-C. The rationale for the dose chosen was based on review of the previous literature and reversal of neurologic deficit in a single PML patient with this regimen. Response with 2-year follow-up and complications of therapy are reported here.

Results

Seven of 19 patients (36%) treated with intravenous ARA-C showed neurologic improvement or stabilization with follow-up (Table 1). All of these seven patients had not progressed at their first neurologic follow-up examination at 3–6 weeks. The shortest interval to clinical neurologic improvement was 4 weeks among the 7 patients. Also, 6 of 7 regained the ability to carry out the activities of daily living, but 4 had obvious residual neurologic disability. In contradistinction, 9 of the 12 who did not respond to ARA-C showed neurologic deterioration and died within 2 months of treatment of their PML.

All patients who improved showed some evidence of radiographic improvement on head MRI scan. Radiographic improvement was not evident, but MRI scans were stable, in eventual improvement patients, done 3–6 weeks after treatment. MRI scans done 2 months to 1 year later did show improvement correlating with clinical findings.

The 12 patients who showed no response deteriorated within 2 months of treatment. All died rapidly after treatment (range, 8 days–6 months—Table 1). In each case, PML-related neurologic disease was the direct or indirect reason for death. In the patients who died, there was no secondary evidence that treatment hastened the demise of these patients. None of the patients exhibited profound anemia, systemic infection, or clinically important hemorrhage.

Table 2 Outcome and PML-associated illness

Improved or stabilized	*Died of PML*
Hodgkin's disease 2/3	Hodgkin's disease 1/3
Non-Hodgkin's lymphoma 1/5	Non-Hodgkin's lymphoma 4/5
	CLL 4/4
SLE 1/1	
Vasculitis 1/1	Sarcoidosis 2/2
	Dermatomyositis 1/1
Heart transplant 1/1	
Liver transplant 1/1	

Grouping patients by outcome and underlying illness, patients with Hodgkin's disease, collagen-vascular disease (systemic lupus erythematosis, vasculitis), and transplant did the best (Table 2). Patients with transplants had their immune suppression regimens altered but not discontinued. Patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), and sarcoidosis did the worst, though numbers of patients in each group was small. One patient with dermatomyositis (patient 18—Tables 1 and 3), had little inflammatory change on her brain biopsy, but easily demonstrated JC virus by *in situ* hybridization, had her azathioprine stopped, and following ARA-C treatment developed neurologic deterioration with marked new gadolinium enhancing lesions on MRI head scan. She died, and at autopsy there was marked perivascular inflammation and little JC virus seen on *in situ* hybridization study.

Toxicity

Patients treated in this study showed evidence of bone marrow toxicity. All patients who survived

Table 1 Clinical outcome

Age/Gender	*Complication of treatment*	*Neurologic outcome*
1.67 M	Pancytopenia requiring transfusion with recovery	Improved, 4.5-year survival
2.64 F	Pancytopenia requiring transfusion with recovery	Improved, 2.9-year survival
3.44 F	Mild pancytopenia	Improved, 3.0-year survival
4.68 F	Mild pancytopenia	Improved, 3.5-year survival
5.75 M	Mild pancytopenia	Improved, died at 14 months of cryptococcal meningitis
6.40 M	Generalized seizure	Stabilized, 2.0-year survival
7.49 F	Mild pancytopenia	Stabilized, died at 14 months of heart failure
8.44 F	Pancytopenia not requiring transfusion	Died in 2 months of PML
9.71 F	Pancytopenia not requiring transfusion	Died in 1.5 months of PML
10.58 M	None	Died in 1 month of PML
11.56 M	Brainstem progression	Died in 8 days of PML
12.42 F	Progressive encephalopathy	Died in 25 days of PML
13.45 F	Pancytopenia not requiring transfusion	Died in 10 days of PML
14.72 F	Leukopenia	Died in 1 month of PML
15.59 M	Mild leukopenia	Died in 6 months of PML
16.59 F	Mild pancytopenia	Died in 2 months of PML
17.47 F	Mild leukopenia	Died in 3 months of PML
18.72 F	Progressive inflammatory encephalopathy	Died in 4 weeks of PML
19.60 M	Mild pancytopenia	Died in 5 months of PML

Abbreviations: M = male, F = female.

Table 3 Clinical characteristics

Age/Gender	*Immunosuppressive illness*	*Neurologic presentation—duration*
1.67 M	Hodgkin's disease	Right UE monoparesis, aphasia—6 months
2.64 F	Cirrhosis, SLE	Pancerebellar syndrome—2 months
3.44 F	Liver transplant	Right cerebellar syndrome—2 months
4.68 F	Vasculitis/MTX/cyclophosphamide	Left hemiparesis—1 month
5.75 M	Lymphoma, history of SLE	Cognitive and personality changes—2 months
6.40 M	Hodgkin's disease	Aphasia, right hemianopsia—2 months
7.49 F	Heart transplant	Cortical blindness—4 months
8.44 F	CLL	Asymmetric cerebellar syndrome—3 months
9.71 F	Sarcoidosis	Left hemiparesis—2 months
10.58 M	Sarcoidosis	Dementia, frontal lobe syndrome—5 months
11.56 M	CLL	Asymmetric cerebellar syndrome—2 months
12.42 F	Hodgkin's disease	Right hemianopsia—7 months
13.45 F	Non-Hodgkin's lymphoma	Left hemiparesis—6 months
14.72 F	Non-Hodgkin's lymphoma	Aphasia, right hemiparesis—2 months
15.59 M	CLL	Right hemianopsia, aphasia—2 months
16.59 F	Non-Hodgkin's lymphoma	Right hemiparesis—5 months
17.47 F	Non-Hodgkin's lymphoma	Cortical blindness—3 months
18.72 F	Dermatomyositis/azathioprine	Cognitive and personality changes—2 months
19.60 M	CLL	Alexia, right hemianopsia—5 months

Abbreviations: M = male, F = female, UE = upper extremity, CLL = chronic lymphocytic leukemia, MTX = methotrexate, SLE = systemic lupus erythematosis.

1 month or longer had reduction in blood cell counts. All blood cellular elements were affected. The nadir occurred at 10 to 18 days after completion of treatment. Two patients survived less than 2 weeks after completing treatment and died because of their neurologic illness. Of the remaining 17 patients, 2 had severe enough pancytopenia to warrant red blood cell and/or platelet transfusions. The mean nadir of blood

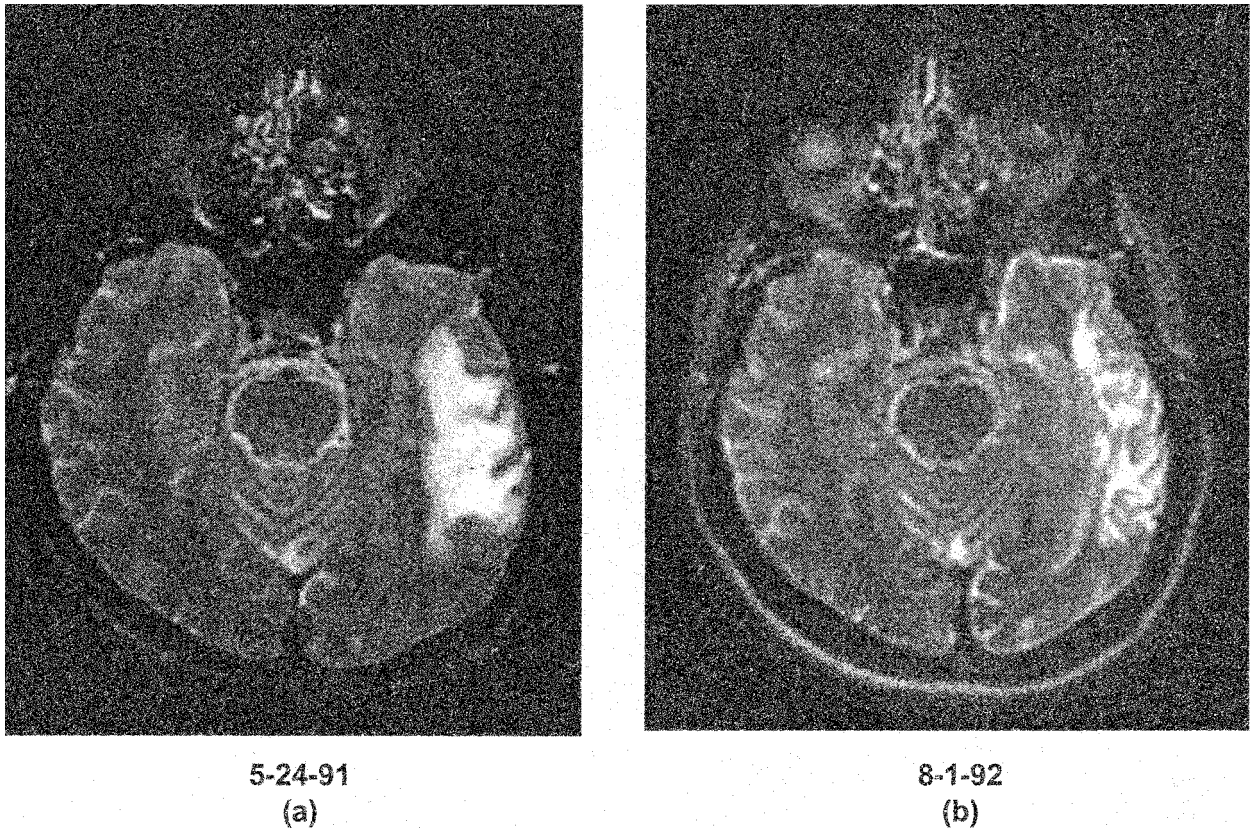

Figure 1 Before (**a**) and after (**b**) treatment with ARA-C, T2-weighted MRI head scans of patient 6 with PML and Hodgkin's. Approximately 14 months elapsed between the scans. The left temporal white matter lesion has improved.

counts were: white blood cells, 3.7×10^9/L (range, 0.6–7.7); hemoglobin, 9.2 g/dL (range, 6.9–12.2); platelets, 108×10^9/L (range, 26–280). All patients who survived their neurologic illness recovered from the bone marrow toxicity.

Discussion

The 36% 1-year survival is higher than expected for a PML patient, based on a prior study that suggested a 1-year survival as low as 10% (Brooks and Walker, 1984). However, the number of patients treated in this open, uncontrolled study is small. In addition, all these patients were referred to tertiary care center, delaying the time between the onset of neurologic symptoms and the initiation of treatment to at least 1 month. This selection bias may have eliminated patients who had a more rapid course. However, the delay may also have lessened the treatment impact, as opposed to treating earlier. Stabilization of previous downhill clinical deterioration was a useful clinical marker of response in the instances where improvement did eventually occur.

Bone marrow toxicity from ARA-C is a limiting factor in the use of this drug in the treatment of PML. PML occurs in the circumstance of immunosuppressive illness such as AIDS, or after patients have been treated with chemotherapeutic agents, leading to pretreatment pancytopenia. When pancytopenia is severe, ARA-C cannot be used, even in the relative low doses as used in this study. Selection for neurologic improvement could also have been a bias in this study because treatment may have been given only to those who were more immunologically preserved.

MRI scan radiographic improvement was not evident in MRI scans performed 3–6 weeks after treatment. However, among the patients who responded, at least subtle MRI changes correlating with clinical improvement did appear later. Improved MRI changes occurred at 2 months or longer after treatment in patients who responded. However, MRI worsening did serve as a marker for progression and lack of response.

Currently, ARA-C given systemically may provide an increased chance for neurologic improvement or stabilization, as used in this study. Treatment was associated with significant bone marrow toxicity, but all patients who survived their neurologic illness recovered. Retreatment after initial round of ARA-C may not be necessary to clear viral infection in some patients (Hall *et al*, 1998). Only a minority of all patients treated in the present study (36%) showed any neurologic response. Only those patients with adequate bone marrow reserves should be considered for therapy if this approach is used.

Materials and methods

Patient characteristics

Patient characteristics are summarized in Table 3. Of the 19 patients reported here, 7 were male and 12 were female. Ages ranged from 40–75 years (mean = 57 years). All presented with focal neurologic symptoms except for 3 patients who presented with dementia and frontal lobe syndromes. The duration of neurologic symptoms before instituting treatment was 1 to 7 months. This length of time reflects uncertainties by primary physicians about diagnosis, the progression of disease, or delay because of brain biopsy. Initial mistaken diagnoses included stroke, metastases to brain, or primary glial neoplasm.

The associated immunosuppressive illnesses are listed in Table 3. Twelve of the nineteen patients had lymphoreticular malignancy. Two had sarcoidosis and one each had systemic lupus erythematosus, vasculitis, dermatomyositis, and heart or liver transplant. The patients had their systemic illness diagnosed 2 months to 14 years prior to development of neurologic symptoms.

Preceding treatment, all patients had a hemoglobin value above 10 g/dL (range, 10.4–14.2). White blood cell count was 3000×10^6/L or above in all patients (range, 3000–143,000). Three patients had very elevated white blood cell count; 2 patients had chronic lymphocytic leukemia, and the third patient had systemic B cell lymphoma with leukemic transformation (white blood cell count range, 46,700–143,000). Accurate CD4/CD8 ratios were available in three patients and were 0.5, 0.5, and 2.0. Absolute CD4 counts ranged from 36/mL to 936/mL. Platelet counts before treatment ranged from 111,000 to $400{,}000 \times 10^6$/L.

Sixteen patients underwent brain biopsy of the focal demyelinated lesion. *In situ* hybridization performed on brain tissue with a biotinylated JC virus–specific probe identified JC virus DNA in infected oligodendrocytes in all 16 patients. All showed intranuclear JC virus DNA replication. Three patients had their PML diagnosed only by spinal fluid polymerase chain reaction (PCR) before treatment.

All patients had brain MRI abnormalities consistent with subcortical cerebral or cerebellar white matter demyelination. Minimal gadolinium enhancement was seen occasionally.

Cytosine arabinoside treatment

All patients were treated unblinded with cytosine arabinoside given intravenously by intermittent infusion of 2 mg/kg per day diluted in 250 milliliters of 5% dextrose and water for each of 5 days (total daily dose range, 90–160 mg/day). Neurologic outcome was judged by detailed neurological examination and MRI head scan, performed 3–6 weeks after treatment. The range of posttreatment follow-up was 2.0–4.5 years for surviving patients.

References

Aksamit AJ Jr (1993). Nonradioactive in situ hybridization in progressive multifocal leukoencephalopathy. *Mayo Clin Proc* **68**(9)**:** 899–910.

Bauer WR, Turel AP Jr, Johnson KP (1973). Progressive multifocal leukoencephalopathy and cytarabine. Remission with treatment. *JAMA* **226**(2)**:** 174–176.

Berger JR, Mucke L (1988). Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology* **38**(7)**:** 1060–1065.

Brooks BR, Walker DL (1984). Progressive multifocal leukoencephalopathy. *Neurol Clin* **2**(2)**:** 299–313.

Clifford DB, Yiannoutsos C, Glicksman M, Simpson DM, Singer EJ, Piliero PJ, Marra CM, Francis GS, McArthur JC, Tyler KL, Tselis AC, Hyslop NE (1993). HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology* **52**(3)**:** 623–625.

Hall CD, Dafni U, Simpson D, Clifford D, Wetherill PE, Cohen B, McArthur J, Hollander H, Yainnoutsos C, Major E, Millar L, Timpone J (1998). Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med* **338**(19)**:** 1345–1351.

Kepes JJ, Chou SM, Price LW Jr (1975). Progressive multifocal leukoencephalopathy with 10-year survival in a patient with nontropical sprue. Report of a case with unusual light and electron microscopic features. *Neurology* **25**(11)**:** 1006–1012.

Lidman C, Lindqvist L, Mathiesen T, Grane P (1991). Progressive multifocal leukoencephalopathy in AIDS. *AIDS* **5**(8)**:** 1039–1041.

Marriott PJ, O'Brien MD, Mackenzie IC, Janota I (1975). Progressive multifocal leucoencephalopathy: remission with cytarabine. *J Neurol Neurosurg Psychiatry* **38**(3)**:** 205–209.

Nicoli F, Chave B, Peragut JC, Gastaut JL (1992). Efficacy of cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* **339**(8788)**:** 306.

O'Riordan T, Daly PA, Hutchinson M, Shattock AG, Gardner SD (1990). Progressive multifocal leukoencephalopathy-remission with cytarabine. *J Infect* **20**(1)**:** 51–54.

Peters AC, Versteeg J, Bots GT, Boogerd W, Vielvoye GJ (1980). Progressive multifocal leukoencephalopathy: immunofluorescent demonstration of simian virus 40 antigen in CSF cells and response to cytarabine therapy. *Arch Neurol* **37**(8)**:** 497–501.

Portegies P, Algra PR, Hollak CE, Prins JM, Reiss P, Valk J, Lange JM (1991). Response to cytarabine in progressive multifocal leucoencephalopathy in AIDS. *Lancet* **337**(8742)**:** 680–681.

Price RW, Nielsen S, Horten B, Rubino M, Padgett B, Walker D (1983). Progressive multifocal leukoencephalopathy: a burnt-out case. *Ann Neurol* **13**(5)**:** 485–490.

Rockwell D, Ruben FL, Winkelstein A, Mendelow H (1976). Absence of immune deficiencies in a case of progressive multifocal leukoencephalopathy. *Am J Med* **61**(3)**:** 433–436.

Saxton C, Gailiunas P Jr, Helderman JH, Farkas RA, McCoy R, Diehl J, Sagalowsky A, Murphy FK, Ross ED, Silva FR (1984). Progressive multifocal leukoencephalopathy in a renal transplant recipient. Increased diagnostic sensitivity of computed tomographic scanning by double-dose contrast with delayed films. *Am J Med* **77**(2)**:** 333–337.

Schlitt M, Morawetz RB, Bonnin J, Chandra-Sekar B, Curtiss JJ, Diethelm AG Jr, Whelchel JD, Whitley RJ (1986). Progressive multifocal leukoencephalopathy: three patients diagnosed by brain biopsy, with prolonged survival in two. *Neurosurgery* **18**(4)**:** 407–414.

Steiger MJ, Tarnesby G, Gabe S, McLaughlin J, Schapira AH (1993). Successful outcome of progressive multifocal leukoencephalopathy with cytarabine and interferon. *Ann Neurol* **33**(4)**:** 407–411.