# Progressive Multifocal Leukoencephalopathy

*Joseph R. Berger, MD*

**Address**
Department of Neurology, University of Kentucky College of Medicine, Kentucky Clinic L-445, Lexington, KY 40536-0284, USA.
E-mail: jrbneuro@pop.uky.edu

**Current Treatment Options in Neurology** 2000, **2:**361–368
Current Science Inc. ISSN 1092-8480


## Opinion statement

- Before embarking on experimental therapies for progressive multifocal leukoencephalopathy (PML), the diagnosis needs to be unequivocally established.
- Improving the underlying immunodeficiency state is the best initial approach to the management of PML. Immunosuppressive therapies should be discontinued when feasible. In the patient with AIDS, highly active antiretroviral therapy should be administered; this appears to prolong survival.
- At present, no therapy has been demonstrated to be effective in a well-designed prospective trial. Cytosine arabinoside, which has demonstrated efficacy in vitro against JC virus, has not been effective when administered intravenously or intrathecally to patients with AIDS and PML. The failure of regimens employing cytosine arabinoside in PML may have been the consequence of inadequate penetration of the drug to sites of infection in the brain. Other drugs with established in vitro activity against JC virus, such as topoisomerase and camptothecin, are poorly tolerated. The use of cidofovir in patients with AIDS and PML remains anecdotal, although it is currently under investigation.
- Interferon alfa may improve survival in patients with AIDS and PML and may have general applicability to PML regardless of the cause of the underlying immunodeficient state.
- Approximately 7% to 9% of patients with PML demonstrate prolonged survival (>12 months) and associated improvement in clinical and radiographic abnormalities in the absence of specific therapy. In patients with AIDS-related PML, prolonged survival correlates with PML as the presenting manifestation of AIDS, higher CD4 T-lymphocyte counts, and contrast enhancement of PML lesions on radiographic imaging. A brisk inflammatory response may also be associated with improved survival.
- The increased understanding of the pathophysiology of JC virus provides hope for the development of curative strategies. The growing number of persons affected with PML has allowed the organization of carefully designed therapeutic trials to address this issue.

## Introduction

In 1958, Astrom, Mancall, and Richardson [1••] described a progressive neurologic syndrome with characteristic neuropathologic findings of demyelination, giant astrocytes, and oligodendrocytes with abnormal nuclei; they named the entity *progressive multifocal leukoencephalopathy*. In 1965, viral particles resembling papovavirus were identified within glial nuclei and were subsequently cultured from the PML–affected brain in glial cell cultures [2,3]. Named JC virus, it is a double-stranded DNA virus of icosahedral symmetry. Its ability to hemagglutinate type O erythrocytes has permitted the performance of seroepidemio-

logic studies, which demonstrate that JC virus infection is worldwide, is common (about 80% of all populations studied), and usually occurs before the age of 20 years. Spread of JC virus is likely via respiratory secretions [4], but no identifiable acute illness has been convincingly established with primary infection. The infection typically remains latent in extra–central nervous system sites until a number of events transpire, chief among them the occurrence of impaired cell-mediated immunity. Until the 1980s, chronic lymphocytic leukemia and lymphoma were the underlying illnesses most often associated with PML. In the past two decades, the frequency of PML has increased dramatically owing to the AIDS epidemic, and it is no longer a rare disease.

Before 1982, 200 cases of PML had been recorded by the National Center for Health Statistics [5,6], most the consequence of lymphoid malignancies. Other neoplastic disorders, granulomatous disease (*eg*, tuberculosis and sarcoidosis), and immunosuppressed conditions were the next most frequent causes [7•]. Since the beginning of the AIDS pandemic, however, the number of persons with PML has increased dramatically. Most studies now report an incidence of approximately 5% in patients with AIDS [8]. In a series from south Florida, a 20-fold increase in the prevalence of PML was seen between the years of 1980 and 1984 and the years 1990 to 1994, with all but 2 of 156 cases of PML occurring in association with HIV [9•]. The number of patients with AIDS developing PML greatly exceeds the rate in other illnesses having similar degrees of impaired cell-mediated immunity, suggesting that factors related to HIV infection may amplify the frequency of the disease.

The JC virus is latent in many extraneural sites, including kidneys, lymph nodes, tonsils, lung, and liver, and likely replicates in bone marrow–derived lymphocytes [10]. It has been postulated that these infected B lymphocytes migrate to the brain, providing the route for central nervous system penetration of the virus [10]. JC virus DNA codes for three capsid proteins, protein "T" (a nonstructural protein responsible for initiation of viral DNA replication and transcription of its capsid proteins), and protein "t," which is of no known pathogenic significance [11••]. Susceptibility to JC virus infection appears to be controlled by cellular transcription factors rather than being dependent on attachment to cellular receptors [11••]. Glial cells are infected because they provide the transcriptional factors necessary for the expression of the virus [10].

The clinical manifestations of PML vary depending on the affected area of white matter. In the AIDS population, common abnormalities include weakness, gait disturbance, speech and language disorders, cognitive dysfunction, and visual loss [9•]. Weakness, frequently hemiparesis, is the foremost manifestation of the disease both at onset and at time of diagnosis. Ataxia, dysarthria, numbness, headaches, aphasia, seizures, and vertigo are occasionally observed [9•]. The frequency with which these clinical findings are seen may be different in the non–AIDS population [7•]. The correct diagnosis of PML is often delayed in persons who are not recognized as having an underlying immunodeficiency state, particularly among those who are not recognized as having HIV infection. PML is rarely present in the absence of detectable focal findings on careful neurologic evaluation.

The diagnosis of PML is strongly supported by radiographic and magnetic resonance imaging studies. On computed tomography, multiple white matter hypodensities are observed, but magnetic resonance imaging is significantly more sensitive [8]. The lesions of PML appear hyperintense on $T_2$ images and hypointense on $T_1$ images [8]. A scalloped appearance in subcortical regions is the consequence of involvement of "U" fibers. There is a predilection for the parieto-occipital region, but about one third of patients with AIDS and PML have posterior fossa involvement [8]. Faint contrast enhancement generally at the periphery of the lesions may be seen in up to 9% [8].

Routine studies of cerebrospinal fluid (CSF) are not particularly helpful in the diagnosis of PML; however, polymerase chain reaction (PCR) for JC virus has become a useful test for diagnosing the disorder [12,13]. The use of PCR for JC virus on cerebrospinal fluid coupled with the appropriate clinical and radiographic studies has assisted in establishing the diagnosis of PML. CSF PCR has a specificity of 100% [14]. Its sensitivity varies from laboratory to laboratory, although some investigators claim the capability of detecting as few as $10^5$ copies per 10 microliters of CSF [15,16]. Since PCR of the cerebrospinal fluid for JC virus is not 100% sensitive, brain biopsy is often required to establish the diagnosis. Confirmation in the absence of a positive CSF PCR for JC virus in the proper clinical and radiologic contexts requires tissue examination. In addition to the pathognomonic histopathologic findings seen on light microscopy, viral particles may be demonstrated by electron microscopy, viral DNA by in situ hybridization, and JC virus antigens by immunocytochemistry.

The prognosis for PML is typically grim, with death occurring in most patients 1 to 18 months (mean 4 months) after disease onset [17,18]. In the setting of AIDS, certain features seem to be associated with a greater likelihood of prolonged survival (more than 12 months): PML as the heralding illness of AIDS; lesser degrees of immunosuppression (CD4 counts of more than 300 cells/$mm^3$); enhancement on radiographic imaging; and any evidence of clinical recovery [19]. Low CSF JC viral loads have also been associated with longer survival [20,21].

# Treatment

- Reversing the immunosuppression that has set the stage for the development of PML should be a high priority. Although this measure is not practical in some conditions (*eg*, HIV infection), if immunosuppression is iatrogenically induced, discontinuing corticosteroid therapy, antineoplastic drugs, or other immunosuppressive agents to allow for the restoration of the immune system may have an ameliorating effect on PML.

## Diet and lifestyle

- There are no compelling reasons or data to suggest that alteration of dietary habits or lifestyle will influence the course of PML. Because the greatest risk factor for the development of PML is HIV infection, alterations in lifestyle may be highly effective in reducing the risk of becoming infected with this virus. Use of injected drugs and having sexual relations with HIV-seropositive partners are the greatest risk factors for acquisition of HIV infection in adults. Avoidance of these activities would substantially reduce the number of patients with PML.

## Pharmacologic treatment

- The treatment of PML remains frustrating because there are no unequivocally successful therapeutic modalities. Before the AIDS epidemic, meaningful studies would have been exceptionally difficult to conduct as a result of the small number of persons with PML. To date, there has been only one well-designed prospective trial of therapy in PML, namely the use of cytosine arabinoside in AIDS-related PML [22•, Class I].
- A not insignificant number of persons have demonstrated remarkable recovery clinically and radiographically in the face of advanced PML [19,23]; it seems that the white matter appears to have the capacity to regain both its structural and its functional integrity if JC virus can be cleared from the brain. Anecdotal evidence based on recovery following restoration of the immune system suggests that the immune system is capable of clearing JC virus from the brain. In addition, in the absence of significant underlying destruction, the brain is capable of remyelinating. An alternative approach to immune reconstitution would be the use of a pharmacologic treatment capable of inhibiting JC virus replication.

### *Cytosine arabinoside*

Because of their ability to impede the synthesis of DNA, nucleoside analogues have been employed in the treatment of PML [24]. In vitro studies [25] have clearly demonstrated the ability of cytosine arabinoside (ara-C) (Cytarabine; Bedford Labs, Bedford, OH), a cytosine analogue, to inhibit JC virus replication; anecdotal reports of intravenous and intrathecal administration suggested the value of this therapy in PML [26–32, Class IIIb]. A carefully conducted clinical trial of AIDS–related PML failed to show the value of either intravenous or intrathecal administration of ara-C when compared with placebo [22•, Class I]. Theoretically, neither method of administration permitted adequate concentrations of the drug to reach the disease sites. More effective methods of drug delivery to the affected intraparenchymal sites may prove that cytosine arabinoside has a role in the treatment of PML; however, this remains unproven.

**Standard dosage** No standard dose for the administration of cytosine arabinoside has been established. In the study by Hall *et al.* [22•, Class I] of AIDS-associated PML, antiretroviral therapy was optimized, and patients in the treatment arms were randomized to receive either intravenous or intrathecal therapy. In the former, cytosine arabinoside was administered as 4 mg/d per kilogram of body weight for 5 days by intravenous infusion followed by a 16-day period when antiretroviral therapy alone was given. This cycle was repeated every 21 days. In the latter, 50 mg of cytosine arabinoside was administered intrathecally through an Ommaya reservoir once a week for 4 weeks; once every 2 weeks for the next 8 weeks; then once every 4 weeks for the remainder of the study without an alteration in antiretroviral therapy.

**Contraindications** Cytosine arabinoside is contraindicated in patients who are hypersensitive to the drug. It is a potent bone marrow suppressant and should be used with extreme caution and careful monitoring, particularly when administered with antiretroviral therapy, which is also toxic to bone marrow.

**Main drug interactions** Cytosine arabinoside causes a reversible decrease in steady-state plasma digoxin concentration and renal glycoside excretion. Therefore, plasma digoxin levels need to be monitored. Also, antibiotic regimens with gentamicin may need to be modified.

**Main side effects** The chief side effect is bone marrow suppression with attendant leukopenia, anemia, and thrombocytopenia. Infectious illness may be observed with the use of cytosine arabinoside, which is a particular concern in the face of a preexisting immunodeficient state.

**Special points** It is likely that the absence of established efficacy of cytosine arabinoside in the treatment of AIDS–associated PML applies to PML arising in other settings as well. Therefore, there exists no compelling reason to recommend its use. The demonstration of its value in suppressing JC viral replication in vitro suggests that more effective drug delivery may lead to restudy of its value.

**Cost/cost effectiveness** In addition to the cost of the medication ($6.75 per 100 mg, average wholesale price) and that of its administration (either intravenous or intrathecal), frequent assessments for bone marrrow suppression are required. When coupled with the absence of compelling data demonstrating the effectiveness of the medication, it is difficult to recommend cytosine arabinoside unless it is administered in an experimental setting with parameters different from those already addressed.

### *Cidofovir*

Cidofovir—1-[(S)-3-hydroxy-2-(phosphomethoxy)propyl]cytosine dihydrate (HPMPC)—and its cyclic counterpart have demonstrated selective antipolyomavirus activity [33]. The 50% inhibitory concentrations for HPMPC are in the range of 4 to 7 μg/mL, and its selectivity index varies from 11 to 20 for mouse polyomavirus and from 23 to 33 for SV40 strains in confluent cell monolayers [33]. It has been proposed as an agent for the treatment of PML [34] because anecdotal cases suggest that it has value in treating PML [35–39, Class IIIb]. Currently, a well-designed AIDS Clinical Trials Group (ACTG) study is addressing the value of cidofovir in the same fashion as it had ara-C earlier. No results are yet available from this study.

**Standard dosage** There is no standard dosage regimen for cidofovir in the treatment of PML. In the ACTG trial, cidofovir is administered in an initial dose of 5 mg/kg, which is repeated on day 7 and then every 14 days thereafter. Adjustments are made for renal function. Probenecid is administered 3 hours before and 2 and 8 hours after each dose of cidofovir, for a total dose of 3 gm for adults weighing 41 to 60 kg and 4 gm for adults weighing more than 60 kg.

**Contraindications** Significant preexisting renal disease would be considered a relative contraindication to the use of cidofovir.

**Main drug interactions** The concomitant administration of nephrotoxic medications (*eg*, intravenous pentamidine, amphotericin B, foscarnet, aminoglycosides, vancomycin, or nonsteroidal anti-inflammatory drugs) should be avoided.

**Main side effects** The principal toxicities of cidofovir are renal, hematologic, and ocular. Renal toxicity is characteristically manifest by elevated serum creatinine level and proteinuria. The chief hematologic side effect is neutropenia. Ocular toxicity is somewhat unique and includes the appearance of hypotony, decreased intraocular pressure, and uveitis.

**Special points** Patients require hydration during the administration of cidofovir. Additionally, intraocular pressure needs to be recorded routinely and the medication discontinued if intraocular pressure drops by more than 50% of pretreatment values.

**Cost/cost effectiveness** This is experimental therapy for which cost effectiveness has not yet been calculated.

### *Interferon alfa*

Occasional positive results have been seen with the use of interferons (IFNs), both subcutaneously [40, Class IIIb] and intrathecally [31, Class IIIb] when used in conjunction with ara-C. The antiretroviral activity of the interferons may be the consequence of their ability to stimulate natural killer cells. In a pilot study of 17 patients with AIDS and PML treated with interferon alfa-2a and zidovudine, 2 had long-term clinical stabilization, though none improved [41, Class IIIa1]. A retrospective study compared patients with AIDS-associated PML receiving a minimum treatment of 3 weeks of 3 million units of IFN-$\alpha$ daily with untreated historical controls and suggested that IFN-$\alpha$ treatment delayed the progression of the disease, palliated symptoms, and significantly prolonged survival [42, Class IIIa2]. Better-designed trials with this agent are clearly warranted.

**Standard dosage** There is no standard dosage for IFN-$\alpha$ in the treatment of PML. The dose employed generally mirrors that used in the treatment of Kaposi's sarcoma occurring in association with AIDS. Three different preparations of IFN-$\alpha$ are currently available. Two forms have been prepared by recombinant technology: interferon alfa-2a (Roferon-A; Roche Laboratories, Nutley, NJ) and interferon alfa-2b (Intron A; Schering Corporation, Union, NJ). A natural preparation of IFN-$\alpha$ is derived from human leukocytes, interferon alfa-N3. The experience accumulated to date has been with the former two preparations; however, they may not be equally effective. Three million units of IFN-$\alpha$ are administered subcutaneously daily. As with AIDS-related Kaposi's sarcoma, the dose may be escalated gradually to 36 million U/d or more.

**Contraindications** Interferon alfa should not be administered to persons with a hypersensitivity to the preparation.

**Main drug interactions** Caution needs to be exercised when administering IFN-$\alpha$ in association with other drugs that cause myelosuppression. Synergistic toxicity has been observed with zidovudine. IFN-$\alpha$ has been found to reduce the clearance of theophylline.

**Main side effects** Constitutional symptoms, including fever, fatigue, headache, chills, anorexia, nausea, diarrhea, and weight loss, are common. Many of the "flulike" constitutional symptoms can be managed with nonsteroidal anti-inflammatory agents. Acute confusion, depression, and suicidal ideation may be observed with use of IFN-$\alpha$.

**Special points** Careful assessment for evidence of myelosuppression needs to be performed periodically during therapy with IFN-$\alpha$. Patients receiving high doses should be cautioned about performing tasks requiring concentration.

**Cost/cost effectiveness** The average wholesale price of IFN-$\alpha$ is approximately $50 per 5 million units. Therefore, the average daily expense for the administration of this medication, assuming lower doses (3 million units), is $30.

### *Adenine arabinoside*

Adenine arabinoside or ara-A (Vidarabine; Monarch Pharmaceuticals, Bristol, TN) [31,43,44, Class IIIb] has been reported to be of anecdotal value in PML. To date, there are no convincing experimental data or well-conducted clinical study results to support its use in PML.

### *Camptothecin*

The antineoplastic drug camptothecin, a DNA topoisomerase I inhibitor, has been demonstrated to block JC virus replication in vitro when administered in pulsed doses in amounts nontoxic to cells [45]. Its therapeutic usefulness in PML has been entirely anecdotal [46,47, Class IIIb].

### *Topotecan*

Another antineoplastic drug, topotecan, may also inhibit JC virus replication [45]. To date, there have been no reports in the literature addressing the experience with topotecan in PML; however, both camptothecin and topotecan display significant systemic toxicity, and their value in the treatment of PML remains highly questionable.

## Interventional procedures

- Power *et al.* [48, Class IIIb] reported remission of AIDS-associated PML following splenectomy in a patient who was receiving antiretroviral therapy. The rationale for the performance of this procedure is not entirely clear, because JC virus had already established a foothold in the brain with the appearance of the clinical and radiographic manifestations of PML. Eliminating the spleen as a potential site of further virus dissemination to the brain seems unwarranted. Whether it has subtle effects on the immunology of PML is uncertain. To date, the success of splenectomy in PML has not been repeated.

## Other treatments/considerations

- Special consideration needs to be given to the treatment of AIDS-associated PML because anecdotal information suggests that antiretroviral therapy, which has no detectable effect on JC virus replication in vitro, may have a salutary effect on PML. As with antiviral therapy being active against JC virus, the current literature purporting effective therapy remains largely anecdotal. Zidovudine (AZT) and other antiretrovirals have been proposed as adjunctive therapy for AIDS-associated PML. One patient has been described with an apparent response to zidovudine [49, Class IIIb], and other investigators have commented on similar cases. In theory, the downregulation of HIV-tat may decrease the transactivation of JC virus. Administration of zidovudine, 1000 mg or more daily, should be attempted in light of its superior ability to cross the blood-brain barrier.
- Perhaps more exciting have been the small retrospective series that have strongly suggested the value of highly active antiretroviral therapy (HAART) in HIV-infected patients with PML [50,51, Class IIIb]. A decrease in the frequency of AIDS-associated PML has been noted since the introduction of HAART [52]. An improvement in survival may not be accompanied by an improvement in neurologic disability consequent to PML [53, Class IIIb]. The benefit of HAART in AIDS-associated PML has not been universally observed, however [54, Class IIIb].

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of special interest
- •• Of outstanding interest


1.•• Astrom K, Mancall E, Richardson E: **Progressive multifocal leukoencephalopathy.** *Brain* 1958, **81:**93–111.

This is a seminal paper in which PML was first clearly described and recognized as a unique illness.

2. Zu Rhein G, Chou S: **Particles resembling papova-viruses in human cerebral demyelinating disease.** *Science* 1965, **148:**1477–1479.

3. Padgett B, Walker DL, ZuRhein GM, *et al.*: **Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy.** *Lancet* 1971, **1:**1257–1260.

4. Monaco MC, Jensen PN, Hou J, *et al.*: **Detection of JC virus DNA in human tonsil tissue: evidence for site of initial viral infection.** *J Virol* 1998, **72(12):**9918–9923.

5. Holman RC, Janssen RS, Buehler JW, *et al.*: **Epidemiology of progressive multifocal leukoencephalopathy in the United States: analysis of national mortality and AIDS surveillance data.** *Neurology* 1991, **41(11):**1733–1736.

6. Moret H, Guichard M, Matheron S, *et al.*: **Virological diagnosis of progressive multifocal leukoencephalopathy: detection of JC virus DNA in cerebrospinal fluid and brain tissue of AIDS patients.** *J Clin Microbiol* 1993, **31(12):**3310–3313.

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

A very good review of PML in the era preceding AIDS.

8. Whiteman ML, Post MJ, Berger JR, *et al.*: **Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation.** *Radiology* 1993, **187(1):**233–240.

9.• Berger JR, Pall L, Lanska D, Whiteman M: **Progressive multifocal leukoencephalopathy in patients with HIV infection.** *J Neurovirol* 1998, **4(1):**59–68.

The largest series of patients with PML ever collected is reported in this paper. The clinical and radiographic features in the AIDS population are described in detail.

10. Houff SA, Major EO, Katz DA, *et al.*: **Involvement of JC virus-infected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy.** *N Engl J Med* 1988, **318(5):**301–305.

11.•• Berger J, Major E: **Progressive multifocal leukoencephalopathy.** In *Textbook of AIDS Medicine.* Edited by Merigan T, Barlett J, Bolognesi D. Baltimore: Williams & Wilkins; 1999:403–420.

An excellent review of JC virus and PML in general.

12. Dorries K, Arendt G, Eggers C, *et al.*: **Nucleic acid detection as a diagnostic tool in polyomavirus JC induced progressive multifocal leukoencephalopathy.** *J Med Virol* 1998, **54(3):**196–203.

13. Cinque P, Vago L, Dahl H, *et al.*: **Polymerase chain reaction on cerebrospinal fluid for diagnosis of virus-associated opportunistic diseases of the central nervous system in HIV-infected patients.** *AIDS* 1996, **10(9):**951–958.

14. Tachikawa N, Goto M, Hoshino Y, *et al.*: **Detection of *Toxoplasma gondii*, Epstein-Barr virus, and JC virus DNAs in the cerebrospinal fluid in acquired immunodeficiency syndrome patients with focal central nervous system complications.** *Intern Med* 1999, **38(7):**556–562.

15. Weber T, Klapper PE, Cleator GM, *et al.*: **Polymerase chain reaction for detection of JC virus DNA in cerebrospinal fluid: a quality control study. European Union Concerted Action on Viral Meningitis and Encephalitis.** *J Virol Methods* 1997, **69(1-2):**231–237.

16. Hammarin AL, Bogdanovic G, Svedhem V, *et al.*: **Analysis of PCR as a tool for detection of JC virus DNA in cerebrospinal fluid for diagnosis of progressive multifocal leukoencephalopathy.** *J Clin Microbiol* 1996, **34(12):**2929–2932.

17. Berger JR, Kaszovitz B, Post MJ, Dickinson G: **Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. A review of the literature with a report of sixteen cases.** *Ann Intern Med* 1987, **107(1):**78–87.

18. von Einsiedel RW, Fife TD, Aksamit AJ, *et al.*: **Progressive multifocal leukoencephalopathy in AIDS: a clinicopathologic study and review of the literature.** *J Neurol* 1993, **240(7):**391–406.

19. Berger JR, Levy RM, Flomenhoft D, Dobbs M: **Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy.** *Ann Neurol* 1998, **44(3):**341–349.

20. Koralnik IJ, Boden D, Mai VX, *et al.*: **JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy.** *Neurology* 1999, **52(2):**253–260.

21. Yiannoutsos CT, Major EO, Curfman B, *et al.*: **Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy.** *Ann Neurol* 1999, **45(6):**816–821.

22.• Hall CD, Dafni U, Simpson D, *et al.*: **Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team.** *N Engl J Med* 1998, **338(19):**1345–1351.

The only well-designed, controlled study of a pharmacologic intervention in PML, demonstrating that cytosine arabinoside is of no value as administered (either intravenously or intrathecally) in this study.

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

24. Goodman A, Gilman A: *The Pharmacological Basis of Therapeutics*, edn 7. New York: MacMillan Publishing Co.; 1985.

25. Hou J, Major E: **The efficacy of nucleoside analogs against JC virus multiplication in a persistently infected human fetal brain cell line.** *J Neurovirol* 1998, **4(4):**451–456.
26. Bauer WR, Turel AP Jr., Johnson KP: **Progressive multifocal leukoencephalopathy and cytarabine. Remission with treatment.** *JAMA* 1973, **226(2):**174–176.
27. Buckman R, Wiltshaw E: **Progressive multifocal leucoencephalopathy successfully treated with cytosine arabinoside [letter].** *Br J Haematol* 1976, **34(1):**153–158.
28. Conomy JP, Beard NS, Matsumoto H, Roessmann U: **Cytarabine treatment of progressive multifocal leukoencephalopathy. Clinical course and detection of virus-like particles after antiviral chemotherapy.** *JAMA* 1974, **229(10):**1313–1316.
29. Lidman C, Lindqvist L, Mathiesen T, Grane P: **Progressive multifocal leukoencephalopathy in AIDS [letter].** *AIDS* 1991, **5(8):**1039–1041.
30. O'Riordan T, Daly PA, Hutchinson M, *et al.*: **Progressive multifocal leukoencephalopathy—remission with cytarabine.** *J Infect* 1990, **20(1):**51–54.
31. Tashiro K, Dai S, Moriwaka F, *et al.*: **Progressive multifocal leucoencephalopathy with magnetic resonance imaging verification and therapeutic trials with interferon.** *J Neurol* 1987, **234(6):**427–429.
32. Van Horn G, Bastian F, Moake J: **Progressive multifocal leukoencephalopathy: failure of response to transfer factor and cytarabine.** *Neurology* 1978, **28:**794–797.
33. Andrei G, Snoeck R, Vandeputte M, DeClercq E: **Activities of various compounds against murine and primate polyomaviruses.** *Antimicrob Agents Chemother* 1997, **41(3):**587–593.
34. Sadler M, Chinn R, Healy J, *et al.*: **New treatments for progressive multifocal leukoencephalopathy in HIV-1–infected patients [letter].** *AIDS* 1998, **12(5):**533–535.
35. De Luca A, Fantoni M, Tartaglione T, Antinori A: **Response to cidofovir after failure of antiretroviral therapy alone in AIDS-associated progressive multifocal leukoencephalopathy.** *Neurology* 1999, **52(4):**891–892.
36. Brambilla AM, Castagna N, Novati R, *et al.*: **Remission of AIDS-associated progressive multifocal leukoencephalopathy after cidofovir therapy [letter].** *J Neurol* 1999, **246(8):**723–725.
37. Dodge RT: **A case study: the use of cidofovir for the management of progressive multifocal leukoencephalopathy.** *J Assoc Nurses AIDS Care* 1999, **10(4):**70–74.
38. Blick G, Whiteside M, Griegor P, *et al.*: **Successful resolution of progressive multifocal leukoencephalopathy after combination therapy with cidofovir and cytosine arabinoside.** *Clin Infect Dis* 1998, **26(1):**191–192.
39. Meylan PR, Vuadens P, Maeder P, *et al.*: **Monitoring the response of AIDS-related progressive multifocal leukoencephalopathy to HAART and cidofovir by PCR for JC virus DNA in the CSF.** *Eur Neurol* 1999, **41(3):**172–174.
40. Steiger MJ, Tarnesby G, Gabe S, *et al.*: **Successful outcome of progressive multifocal leukoencephalopathy with cytarabine and interferon.** *Ann Neurol* 1992, **32(4):**407–411.
41. Berger J, Pall L, Mc Arthur J, *et al.*: **A pilot study of recombinant alpha 2a interferon in the treatment of AIDS-related progressive multifocal leukoencephalopathy [abstract].** *Neurology* 1992, **42(suppl 3):**257.
42. Huang SS, Skolasky RL, DalPan GJ, *et al.*: **Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study.** *J Neurovirol* 1998, **4(3):**324–332.
43. Rand KH, Johnson KP, Rubinstein LJ, *et al.*: **Adenine arabinoside in the treatment of progressive multifocal leukoencephalopathy: use of virus-containing cells in the urine to assess response to therapy.** *Ann Neurol* 1977, **1(5):**458–462.
44. Wolinsky JS, Johnson KP, Rand K, Merigan TC: **Progressive multifocal leukoencephalopathy: clinical pathological correlates and failure of a drug trial in two patients.** *Trans Am Neurol Assoc* 1976, **101:**81–82.
45. Kerr DA, Chang CF, Gordon J, *et al.*: **Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin.** *Virology* 1993, **196(2):**612–618.
46. Vollmer-Haase J, Young P, Ringelstein EB: **Efficacy of camptothecin in progressive multifocal leucoencephalopathy [letter].** *Lancet* 1997, **349(9062):**1366.
47. O'Reilly S: **Efficacy of camptothecin in progressive multifocal leucoencephalopathy [letter].** *Lancet* 1997, **350(9073):**291.
48. Power C, Nath A, Aoki FY, Bigio MD: **Remission of progressive multifocal leukoencephalopathy following splenectomy and antiretroviral therapy in a patient with HIV infection [letter].** *N Engl J Med* 1997, **336(9):**661–662.
49. Conway B, Halliday WC, Brunham RC: **Human immunodeficiency virus–associated progressive multifocal leukoencephalopathy: apparent response to 3′-azido-3′-deoxythymidine.** *Rev Infect Dis* 1990, **12(3):**479–482.
50. Inui K, Miyagawa H, Sashihara J, *et al.*: **Remission of progressive multifocal leukoencephalopathy following highly active antiretroviral therapy in a patient with HIV infection.** *Brain Dev* 1999, **21(6):**416–419.
51. Tantisiriwat W, Tebas P, Clifford DB, *et al.*: **Progressive multifocal leukoencephalopathy in patients with AIDS receiving highly active antiretroviral therapy.** *Clin Infect Dis* 1999, **28(5):**1152–1154.
52. Ledergerber B, Egger M, Erard V, *et al.*: **AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study.** *JAMA* 1999, **282(23):**2220–2226.
53. Gasnault J, Taoufik Y, Goujard C, *et al.*: **Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy.** *J Neurovirol* 1999, **5(4):**421–429.
54. De Luca A, Ammassari A, Cingolani A, *et al.*: **Disease progression and poor survival of AIDS-associated progressive multifocal leukoencephalopathy despite highly active antiretroviral therapy [letter].** *AIDS* 1998, **12(14):**1937–1938.