Failure of Cidofovir Therapy in Progressive Multifocal Leukoencephalopathy Unrelated to Human Immunodeficiency Virus

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We describe the first reported human immunodeficiency virus (HIV)-seronegative patient treated with cidofovir for progressive multifocal leukoencephalopathy (PML). Marked clinical and radiological progression of PML occurred during cidofovir therapy. The improvement observed during cidofovir therapy of HIV-infected patients may be due to the effect of concomitant antiretroviral therapy rather than cidofovir.

Progressive multifocal leukoencephalopathy (PML) was an extremely rare disease before the emergence of the epidemic of HIV. Currently, most cases of PML occur in patients with advanced HIV disease. Although PML is now known to be caused by a papovavirus, there is no therapy of proven efficacy. On the basis of anecdotal reports and uncontrolled experience, cytarabine was thought to have therapeutic efficacy in the treatment of PML, but a recent controlled study showed that it had no benefit [1]. Few other therapeutic agents look promising. In patients with HIV, the survival rate increases [2, 3], and the clinical and radiological features of PML may improve [4] after antiretroviral therapy (ART).

Cidofovir shows efficacy against JC virus (JCV) in vitro [5]. A recently published summary of a study of 22 patients, all of whom were infected with HIV, describes improvement in 16 patients, worsening in 4, and no change in 2 [6–12]. Although information either on the ART or on indicators of response to HIV treatment was not consistently provided, it appears that all patients received at least some ART, and most, if not all, were treated during the era of highly active ART.

We report an experience with the use of cidofovir for the treatment of a patient who had chronic lymphocytic leukemia as the factor predisposing to PML. A 64-year-old woman had a 5-year history of chronic lymphocytic leukemia. Therapy had included chlorambucil, fludarabine, and splenectomy, and her treatment course had been complicated by clostridial myonecrosis of the leg 5 months previously as well as by suspected pulmonary aspergillosis, the latter having been treated with itraconazole. For several months before her admission to the hospital, her only therapy had been monthly doses of iv immunoglobulin.

The patient presented with right hemiparesis and facial weakness that progressed gradually over 1 month. When we examined her, we found that she had complete loss of movement of the right arm, grade I–II/VI strength in the right leg, a right upper motor neuron facial palsy, and dysarthria. MRI scans showed a single nonenhancing lesion without mass effect in the left parietal lobe, internal capsule, and thalamus (figure 1). A stereotactic brain biopsy specimen revealed histologic features characteristic of PML, and in situ hybridization demonstrated JCV DNA in many glial cell nuclei. Results of HIV serological tests were negative.

After extensive discussion with the patient and her family, we agreed upon a trial of 12 weeks of cidofovir (provided by Pharmacia and Upjohn). She received the first 2 doses of 5 mg/kg 1 week apart, and subsequent doses at 2 week intervals, each preceded by probenecid and iv saline.

Therapy was tolerated relatively well, but proteinuria of grades 1 and 2 was noted before the penultimate dose and the last dose, respectively. Serum levels of creatinine remained normal and stable throughout treatment. Altogether, she received 5 doses of 5 mg/kg and 1 dose of 3 mg/kg, the latter having been reduced because of the proteinuria.

During the course of treatment, she demonstrated steady clinical progression, with further deterioration of speech. At no time were there any objective indications of improvement. A repeat MRI scan taken 12 weeks after she started treatment showed marked progression (figure 2), with enlargement of the initial lesion and development of new foci of involvement in the cerebellum.

Published experience with cidofovir in PML has been limited to case reports about HIV-infected patients. To our knowledge, the patient we studied is the first HIV-seronegative patient reported to have been treated with cidofovir for this disease. She had not received any therapy that was likely to have had a major effect on immune responsiveness, either immediately
before or during cidofovir treatment. She experienced striking clinical and radiological progression of her disease in spite of having received a course of cidofovir therapy sufficient to have been associated with a response in previously reported cases.

Data from previously reported patients who received cidofovir treatment for PML are difficult to interpret because of the variable natural history of PML and the likelihood of publication bias in early case reports about a new therapy. Perhaps, most importantly, it is impossible to separate the possible effects of cidofovir from those of ART in these cases. Because of the absence of the complicating factor of ART and any immunological changes that might have resulted from it in the patient we studied, we believe that her experience is more reflective of the true benefit of cidofovir in PML than are the experiences of previously reported, HIV-seropositive patients.

As was the case with cytarabine, a controlled trial will be necessary in order to assess the therapeutic efficacy of cidofovir in patients with PML. Because a sufficient number of HIV-seronegative patients is unlikely to be found for one to answer this question, a study with an adequate sample size of HIV-seropositive patients, which pays careful attention to controlling for ART and immunological response to therapy, will be needed.

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References