Cidofovir and Foscarnet for Treatment of Human Herpesvirus 6 Encephalitis in a Neutropenic Stem Cell Transplant Recipient

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We report a stem cell transplant recipient who developed human herpesvirus 6 encephalitis. Human herpesvirus 6 load indicated massive intrathecal viral replication. Administration of cidofovir followed by foscarnet was associated with total clearance of human herpesvirus 6 infection. Cidofovir and foscarnet combination therapy may be beneficial for reducing mortality of (neutropenic) stem cell transplant recipients with human herpesvirus 6 encephalitis.

Human herpesvirus 6 (HHV-6) is the etiologic agent of exanthema subitum, a febrile rash illness that can occur during early childhood and that is occasionally accompanied by convulsions. After resolution of primary infection, HHV-6 remains latent in the host and may reactivate during immunosuppression [1], inducing end-organ diseases.

In transplant recipients, HHV-6 infection or reactivation occurs at a frequency of 30%–50% [1], with a viral load peak occurring at 2–4 weeks after transplantation [2]. HHV-6 reactivation is associated with encephalitis, bone marrow suppression, and allograft rejection. Encephalitis is the most frequently reported clinical manifestation [1], with mortality exceeding 50% [3].

Ganciclovir, foscarnet, and cidofovir (CDV) inhibit HHV-6 replication in vitro [4] and are currently used for patients experiencing HHV-6–associated end-organ disease. Data on suppression of HHV-6 replication in vivo are mainly based on case studies [5], because controlled therapeutic trials of HHV-6–associated end-organ disease are lacking. In this context, standardized protocols for efficient treatment of HHV-6 infection are urgently needed.

Case report. A 47-year-old man received a diagnosis of B-cell chronic lymphocytic leukemia, with initial clinical stage Binet A. After experiencing an early relapse of B-cell chronic lymphocytic leukemia after receiving fludarabine therapy, the patient was referred for unrelated allogeneic peripheral blood stem cell transplantation. Pretransplantation conditioning included fludarabine, alemtuzumab, and busulfan therapies. Prophylaxis for graft-versus-host disease was initially implemented with cyclosporin A but was switched to tacrolimus because of the occurrence of adverse effects.

On day 22, grade II graft-versus-host disease of the skin developed, but it responded well to prednisolone therapy. One week later, the patient presented with persistent headache, discrete tremor, confusion, short-term memory dysfunction, and altered mental status. He was given oral acyclovir for clinical suspicion of herpes simplex encephalitis.Biochemical analysis of lumbar CSF revealed mild lymphocytic pleocytosis (lymphocyte count, 39 cells/mm3; normal lymphocyte count, <5 cells/mm3) and a slight increase in glucose level (8.35 mmol/L; normal range, 2.8–4.4 mmol/L), total protein level (446 mg/L; normal range, 130–400 mg/L), and lactate level (4.14 mmol/L; normal range, 1.2–2.1 mmol/L). An MRI of the brain (figure 1) showed high signal intensity in the bilateral hippocampus and parahippocampus, consistent with encephalitis. The MRI was performed on day 22.

Figure 1. Axial brain MRI in T1-weighted (left panel) and T2-weighted (right panel) sequences. High signal intensity in bilateral hippocampus and parahippocampus is slightly asymmetric and more pronounced on the left, confirming diagnosis of encephalitis. The MRI was performed on day 22.
Famciclovir are currently being used for treatment of Herpesvirus infections. In particular, acyclovir, ganciclovir, cidofovir, brivudine, and penciclovir and are widely approved for treatment of HHV-6–associated disease. The clinical picture of our patient was dominated by severe impairment of short-term memory function and by recurrent seizures. Nonenhancing lesions in the hippocampus and parahippocampus areas revealed by brain MRI (figure 1) and CSF positive for HHV-6 confirmed the diagnosis. To date, standardized therapy of HHV-6 infection in immunosuppressed patients is lacking, and no drug has been widely approved for treatment of HHV-6–associated disease. Acyclovir, ganciclovir, cidofovir, brivudine, and penciclovir and famiclovir are currently being used for treatment of Herpesviridae infections [7]. Because HHV-6 lacks a thymidine kinase, it is insensitive to acyclovir at achievable serum concentrations, making the use of acyclovir inadequate [4]. A prerequisite for successful treatment of HHV-6 encephalitis is to achieve therapeutic concentrations in the CSF. Ganciclovir is currently used as first-line therapy for HHV-6 encephalitis. However, limited success of ganciclovir therapy in preventing fatal outcome has been reported. In the patients who experienced a fatal outcome, ganciclovir did not achieve a reduction of HHV-6 load in CSF [8], although drug penetration into the CSF was reported [9]. The myelotoxicity of ganciclovir may hamper its use in (neutropenic) bone marrow and stem cell transplant recipients.

CDV displays efficacy against several DNA viruses (i.e., Adenoviridae, Herpesviridae, and Polyomaviridae) and shows strong in vitro activity against HHV-6 [4]. CDV is not myelosuppressive, like ganciclovir, but has distinct renal toxicity. Clinical experience of CDV in the treatment of HHV-6 encephalitis is restricted to few case studies with contradictory results regarding its therapeutic effectiveness [10, 11]. Foscarnet has antiviral activity against all herpesviruses, including HHV-6 [4]. Clinical and experimental studies have reported a good penetration of foscarnet into the CNS [12]. Drug concentrations measured in CSF and brain tissue were either within the range of the 50% inhibitory concentrations or reached levels far above this threshold [12]. Foscarnet is more nephrotoxic but less myelotoxic than ganciclovir. Case reports have documented both successful and disappointing results of foscarnet treatment for HHV-6 encephalitis in transplant recipients [3, 5, 8].

In our patient, there was evidence of a significant reduction in HHV-6 load in CSF and in plasma after CDV administration. Of note, our patient had a normal albumin quotient, excluding an impairment of the blood-brain barrier. According to the manufacturer’s instructions (Gilead Sciences), CDV does not diffuse into the CSF, and detailed studies on the pharmacokinetics of CDV are lacking. The detection of HHV-6 DNA in the CSF of immunodeficient patients has to be interpreted cautiously, because diapedesis of latently infected peripheral blood lymphocytes in the CNS may mimic active infection. The high viral load (396,575 genome equivalents per mL) measured in our patient’s CSF points toward an intrathecal HHV-6 reactivation. A CSF viral load of that magnitude was not caused by exclusive cellular passage, especially because lymphocytic pleocytosis was discrete (lymphocyte count, 39 cells/mm³). During viremia, diffusion is a possible pathway for free virus to enter the CNS. Under steady-state conditions, a viral load that is higher in CSF than in peripheral blood is consistent with active viral replication within the CNS or with diffusion...
(if the kinetics of virus clearance from the CSF are slower than the kinetics of virus clearance from peripheral blood).

The significant decrease of CSF HHV-6 load after administration of CDV in our patient remains to be confirmed in controlled clinical trials. Because of worsening of the clinical status (i.e., the occurrence of seizures) and the limited experience with CDV for treatment of viral CNS infections, therapy was switched to foscarnet on day 35. The patient’s creatinine level and renal function showed no abnormalities during CDV or foscarnet treatment.

Both entry of free virus particles into the CNS because of viremia and reactivation from CNS cells harboring HHV-6 may contribute to the genesis of encephalitis. CDV, the drug with the strongest in vitro activity against HHV-6 [4], reduces the possibility of free virus entering the CNS and infecting potential target cells by lowering HHV-6 plasma load, and foscarnet, with its good CNS penetration ability [12], inhibits HHV-6 replication at the site of infection. Therefore, the combination of CDV and foscarnet for treatment of HHV-6 encephalitis in neutropenic bone marrow and stem cell transplant recipients is a reasonable approach and is worth being evaluated in randomized trials, with the prerequisite that renal function is thoroughly monitored.

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References