Development of Herpes Simplex Virus Stomatitis during Receipt of Cidofovir Therapy

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We report 3 children who, after undergoing hematopoietic stem cell transplant, developed herpes simplex virus (HSV) stomatitis while receiving weekly cidofovir as preemptive treatment for cytomegalovirus infection. All patients responded well to treatment with either acyclovir or ganciclovir. Despite the in vitro susceptibility of HSV to cidofovir, once-weekly treatment with this agent may not be adequate prophylaxis in pediatric patients.

Use of cidofovir, a nucleotide analogue antiviral agent, is increasing in pediatric patients undergoing hematopoietic stem cell transplant (HSCT) to treat infection with cytomegalovirus (CMV) [1], adenovirus [2–7], and BK virus [8, 9]. Two different dosing strategies exist: 5 mg/kg once a week [1–3, 7, 8, 10, 11] and 1 mg/kg 3 times a week [4–6, 9]. Cidofovir can also be used to treat infection with acyclovir-resistant herpes simplex virus type 1 (HSV-1) [8, 10, 11]. However, we now report 3 children who developed HSV-1 stomatitis while receiving weekly cidofovir to treat reactivation of CMV infection.

Patient 1. An 11-year-old HSV-1–seropositive boy received an 8/8 HLA-matched allogeneic bone marrow transplant from an unrelated donor for treatment of acute lymphoblastic leukemia in third complete remission. His conditioning regimen consisted of 1350 cGy of total body irradiation, cyclophosphamide, and equine antithymocyte globulin. Before transplant, both the patient and his donor were noted to be CMV seropositive. One month after transplant, he developed CMV viremia (1500 copies/mL), which was preemptively treated with ganciclovir (5 mg/kg twice a day for 3 weeks then once a day for 12 weeks). Four months after transplant, he developed acute and then progressive-onset extensive chronic graft-versus-host disease (GVHD) of the skin. His chronic GVHD was managed with oral prednisone (1 mg/kg alternating with 0.65 mg/kg every other day), mycophenolate mofetil (15 mg/kg by mouth twice a day; most recent mycophenolate acid level, 1.7 μg/mL), and topical corticosteroids. While receiving immunosuppression for treatment of chronic GVHD, he received prophylactic oral acyclovir (400 mg/m² twice a day).

Twelve and a half months after HSCT, polymerase chain reaction (PCR) revealed a CMV load of 1240 copies/mL. Because the patient had a history of moderate pancytopenia secondary to either GVHD or medications and to avoid additional myelosuppression associated with ganciclovir therapy, cidofovir was started (5 mg/kg once a week, given with probenecid), and prophylactic acyclovir was discontinued (Figure 1A). Fourteen days later (13 months after HSCT), he presented with a 3-day history of mouth sores. A culture of one of the oral lesions grew HSV-1. Oral acyclovir (400 mg/m² three times a day) was restarted, and the oral lesions resolved over the course of 3 days. He received concomitant acyclovir and cidofovir for 3 weeks without elevation in his serum creatinine level. By this time, he had become negative for CMV by PCR, so cidofovir was discontinued and acyclovir was decreased back to a twice-daily dose. At the time of writing, 26 months had passed since the HSCT, and his chronic GVHD was slowly improving.

Patient 2. A 7-year-old HSV-1–seropositive boy received a 7/8 HLA-matched allogeneic bone marrow transplant from an unrelated donor for treatment of hypodiploid acute lymphoblastic leukemia in second complete remission. His conditioning regimen was identical to that of patient 1. His acute GVHD prophylaxis consisted of cyclosporine and methotrexate. He experienced severe HSV stomatitis on 2 occasions after consolidation chemotherapy, for which he had twice received a 7-day course of acyclovir (10 mg/kg/dose 3 times a day). Before transplant, both the patient and his donor were noted to be CMV seropositive. One month after transplant, he developed CMV viremia (1500 copies/mL), which was preemptively treated with acyclovir (400 mg/m² twice a day). Four months later (13 months after HSCT), he presented with a fever and 2 days later (13 months after HSCT), he presented with a 3-day history of mouth sores. A culture of one of the oral lesions grew HSV-1. Oral acyclovir (400 mg/m² three times a day) was restarted, and the oral lesions resolved over the course of 3 days. He received concomitant acyclovir and cidofovir for 3 weeks without elevation in his serum creatinine level. By this time, he had become negative for CMV by PCR, so cidofovir was discontinued and acyclovir was decreased back to a twice-daily dose. At the time of writing, 26 months had passed since the HSCT, and his chronic GVHD was slowly improving.

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Figure 1. Timing of use of antiviral agents in 3 pediatric hematopoietic stem cell transplant recipients in relation to reactivation of cytomegalovirus (CMV) infection and development of stomatitis. Note the difference in scale between panels A (months) and B (weeks). ACV, acyclovir; CDV, cidofovir; FOS, foscarnet; GCV, ganciclovir; PCR, polymerase chain reaction.

Nineteen days after HSCT, he developed lesions on his lips. A culture of one of the oral lesions grew HSV-1. The minimum inhibitory concentration (MIC) for acyclovir was 1.6 μg/mL (susceptible), and the MIC for foscarnet was 50 μg/mL (susceptible) (Focus Technologies). By day 22, he had evidence of neutrophil engraftment, so cidofovir was discontinued and ganciclovir (5 mg/kg given intravenously twice a day) was started (Figure 1B). The oral lesions rapidly resolved, and both the CMV load and the HHV-6 load became undetectable by PCR by day 46. The patient required twice-weekly granulocyte colony-stimulating factor therapy during this time to maintain an absolute neutrophil count of >1 × 10⁹ cells/L. Ganciclovir therapy was decreased to once daily for an additional 4 weeks, and prophylactic acyclovir was restarted. At the time of writing, 9 months had passed since the HSCT, and the patient was doing well.

Patient 3. A 3-year-old HSV-1–seropositive boy received a 5/8 HLA-matched haplocompatible T cell–depleted peripheral blood stem cell transplant from his mother for treatment of juvenile myelomonocytic leukemia. His conditioning regimen consisted of 1200 cGy of total body irradiation, fludarabine, thiotepa, and rabbit equine antithymocyte globulin. Before
transplant, both the patient and his donor were noted to be CMV seropositive. His routine posttransplant antiviral prophylaxis consisted of intravenous foscarnet (60 mg/kg twice a day) from day 1 to 21, followed by oral acyclovir (500 mg/m² three times a day). On day 27 after transplant, PCR revealed a CMV load of 600 copies/mL. Repeat PCR demonstrated 1000 CMV copies/mL on day 35. Acyclovir was discontinued on day 29, and he was initially treated with intravenous ganciclovir (5 mg/kg twice a day) for 4 days; however, this was stopped because of a decreasing absolute neutrophil count. Cidofovir (5 mg/kg once a week, given with probencid) was started on day 33 (Figure 1B).

Forty-eight days after HSCT, he presented with a 4-day history of mouth sores. A culture of one of the oral lesions grew HSV-1. Oral acyclovir (500 mg/m² three times a day) was restarted, and the oral lesions rapidly resolved. He received concomitant acyclovir and cidofovir for 6 weeks, with resolution of CMV viremia and without elevation in his serum creatinine level. At the time of writing, 6 months had passed since the HSCT, and he was receiving additional chemotherapy and immunotherapy to treat progression of his juvenile myelomonocytic leukemia.

Discussion. Because of its lack of significant myelosuppression, cidofovir is an attractive anti-CMV agent for use in pediatric HSCT recipients who cannot tolerate ganciclovir. In addition, it is the only known agent with in vitro activity against adenoviral infections. Because of the in vitro susceptibility of HSV to cidofovir as well as overlapping nephrotoxicity, clinicians initiating cidofovir therapy may elect to discontinue acyclovir prophylaxis with the expectation that cidofovir will also serve to prevent reactivation of HSV infection. However, we have now observed 3 pediatric patients who developed culture-proven HSV-1 stomatitis after prophylactic acyclovir was stopped and during receipt of once-weekly cidofovir.

One possible explanation for this finding would be that all 3 patients harbored cidofovir-resistant HSV strains; however, this seems unlikely, because they had been receiving cidofovir therapy for only 7–12 days at the time when stomatitis developed. All 3 patients had previously been treated with acyclovir and/or ganciclovir. The mechanism of resistance to these agents is generally mutations in the viral thymidine kinase, whereas HSV resistance to cidofovir appears to be mediated through mutations in the viral DNA polymerase, so that cross-resistance is rare [12, 13]. However, patient 3 did receive 21 days of foscarnet, resistance to which is mediated by mutations in the DNA polymerase, making it a potential mechanism by which this patient’s HSV-1 infection developed during receipt of cidofovir. Unfortunately, cidofovir susceptibility testing of the HSV-1 samples from our patients was not performed, because the isolates were no longer available. Wyles et al [13] reported 3 adults who developed cidofovir-resistant HSV disease after chemotherapy or HSCT. The 50% inhibitory concentration for cidofovir was elevated in all 3 patients, and acyclovir resistance (both in vitro and in vivo) was also noted in 2 of the patients [13]. Similar to all 3 of our patients, the third patient responded well to acyclovir [13].

Alternately, it is possible that the pharmacokinetics of once-weekly cidofovir therapy in children is not adequate to prevent reactivation of HSV infection. To the best of our knowledge, studies of the pharmacokinetics of cidofovir in children have not been conducted, and the currently used dosing regimens are based on adult trials. Of note, one group observed a case of asymptomatic HSV infection 2 weeks into a course of cidofovir (1 mg/kg 3 times a week) for treatment of adenovirus infection. Unlike our 3 patients, this patient was not treated and never developed signs of HSV disease [5]. However, another group reported that 2 of 16 patients receiving cidofovir 3 times a week developed HSV stomatitis [6]. Conversely, Le- grand et al [7] reported that 1 of 7 patients treated with once-weekly cidofovir developed oral necrotic HSV lesions. However, other groups using once-weekly cidofovir in pediatric patients have not commented on problems with reactivation of HSV infection [1–3], although one group specifically reported resumption of prophylactic acyclovir 4 days after cidofovir infusions [3]. This may reflect a difference in HSV suppression between the once-weekly and thrice-weekly dosing regimens. Interestingly, 3 children infected with acyclovir- and/or foscarnet-resistant HSV-1 have been successfully treated with once-weekly cidofovir [8, 10, 11]. Therefore, the exact mechanism by which HSV-1 stomatitis developed in our patients during receipt of cidofovir is unclear. Future pediatric trials of cidofovir will hopefully clarify its pharmacokinetics in children and determine the optimal dosing strategy. Careful monitoring for breakthrough HSV-1 infection should be performed.

In conclusion, clinicians using cidofovir should be aware that the once-weekly dosing regimen may not be sufficient to prevent reactivation of HSV-1 infection in pediatric patients. Despite potentially overlapping nephrotoxicity, continuation of prophylactic acyclovir should be considered; at the very least, clinicians should carefully monitor for symptoms and intervene promptly if necessary.

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References