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Case Report

Brincidofovir for Polyomavirus-Associated Nephropathy After Allogeneic Hematopoietic Stem Cell Transplantation

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Polyomavirus-associated nephropathy (PVAN) is common in patients who have undergone kidney transplantation and has been reported in hematopoietic stem cell (HSC) transplant recipients. Aside from reduction of immunosuppression, few therapeutic options exist for treatment of PVAN. We report a case of PVAN in a severely immunocompromised allogeneic HSC transplant recipient that was treated with brincidofovir without reduction of immunosuppression. We review our institutional experience of PVAN in HSC transplantation and discuss the potential use of brincidofovir for treatment.
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INDEX WORDS: Polyomavirus-associated nephropathy (PVAN); BK virus; BK viremia; kidney failure; hematopoietic stem cell (HSC) transplantation; brincidofovir.

BK virus, a member of the *Polyomavirus* genus, is a known cause of transplant dysfunction in up to 10% of kidney transplant recipients.[1,2] Polyomavirus-associated nephropathy (PVAN) also has been reported in native kidneys of nonrenal solid-organ transplant recipients and hematopoietic stem cell (HSC) transplant recipients.[3-8] Kidney biopsy remains the gold standard for the diagnosis of PVAN; the presence of intranuclear BK virus inclusion bodies, which stain positive for the large T antigen, is pathognomonic for PVAN.[9]

BK viremia is associated with the development of PVAN in kidney transplants and thus kidney transplant recipients are screened routinely for BK viremia.[2] However, BK viremia is not monitored routinely after HSC transplantation because the prevalence of PVAN and the relative contribution of BK virus to reduced kidney function after HSC transplantation are not well defined. Further, multiple other factors are likely to contribute to reduced kidney function after HSC transplantation, including radiation, calcineurin inhibitors, and infections. Even so, BK viremia has been implicated in kidney failure and PVAN after HSC transplantation in at least 2 studies.[10,11] In another study in HSC transplant recipients, 3 of 20 kidney biopsy specimens showed evidence of PVAN, a sign that this complication might be more prevalent than previously thought.[12] All 3 patients had BK viremia, and the pathology findings showed diffuse interstitial inflammation and tubulitis. Marked nuclear enlargement and intranuclear inclusions were seen in many tubular cell nuclei. The presence of BK virus was confirmed by positive nuclear immunohistochemical staining using antibodies against the large T antigen of the closely related polyomavirus simian virus 40 (SV40; antibodies to SV40 large T cross-react with the analogous antigen of BK virus).[12]

Although the decrease in maintenance immunosuppression may prevent the progression of PVAN in kidney transplant recipients,[2] the majority of reported cases of PVAN in HSC transplant recipients required hemodialysis due to progressive kidney failure.[4]

Brincidofovir is an orally bioavailable lipid acyclic nucleoside phosphonate that undergoes intracellular conversion to cidofovir diphosphate.[13] Brincidofovir has been shown to have activity against BK virus in renal tubular cells, and in vivo animal distribution studies have demonstrated high concentrations of total drug-related material in the kidney after oral administration of radiolabeled brincidofovir.[13-15] However, unlike cidofovir, brincidofovir is not a substrate for the organic anion transporter, which is located in proximal renal tubules. Consequently, brincidofovir is not concentrated in proximal tubules

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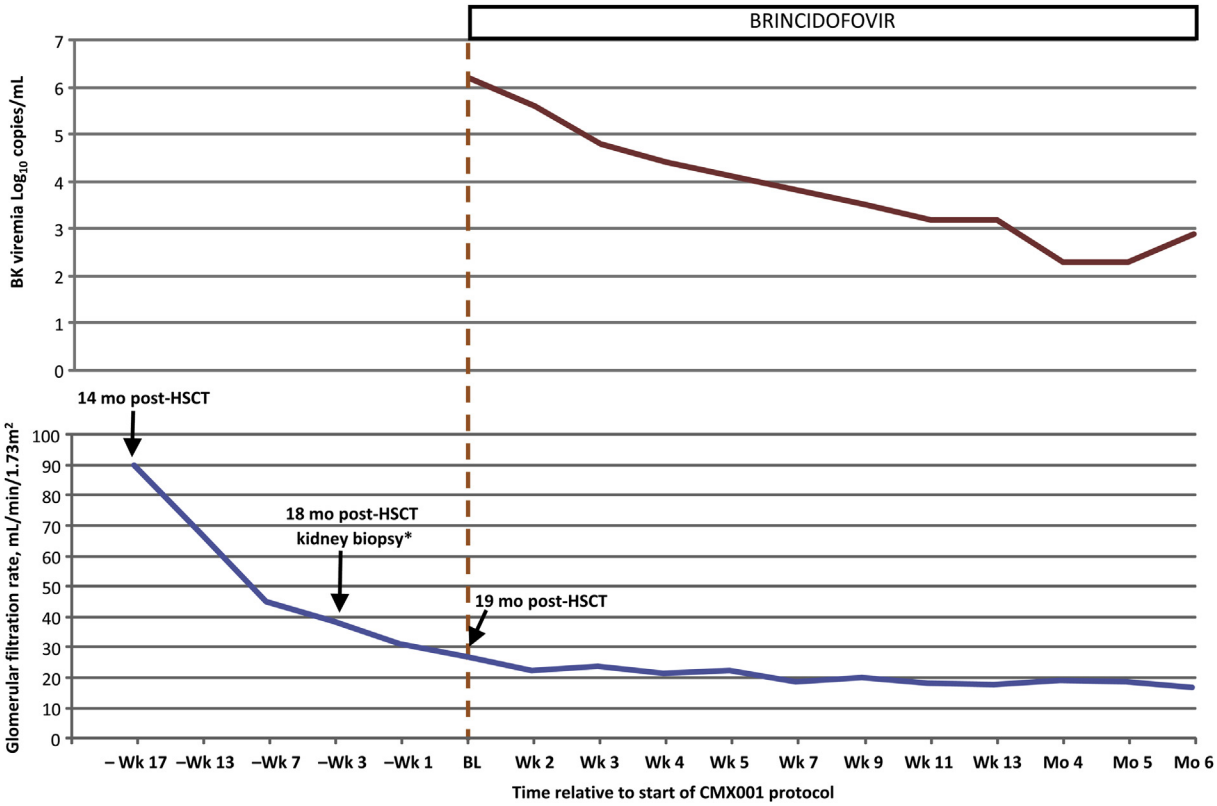

Figure 1. (Upper panel) Plasma BK viremia and (lower panel) estimated glomerular filtration rate (eGFR) in patient 1. *Time is not to scale; baseline (BL) is the first day of brincidofovir treatment in the open-label study CMX001-350. eGFR was calculated using the 4-variable isotope-dilution mass spectrometry–traceable MDRD (Modification of Diet in Renal Disease) Study equation.[17] Abbreviation: HSCT, hematopoietic stem cell transplantation.

and has not been reported to cause kidney toxicity in preclinical or clinical trials.[13,15,16]

We report a case of PVAN in a severely immunocompromised HSC transplant recipient that was treated with brincidofovir without reduction of immunosuppression. We also review our institutional experience of PVAN in HSC transplantation and discuss the potential use of brincidofovir for treatment.

CASE REPORT

A 58-year-old white man with a history of diffuse large B-cell lymphoma received a T-cell–depleted HSC transplant from a matched unrelated donor. Twenty-one days posttransplantation, the patient was enrolled in a randomized trial of brincidofovir for the prevention of cytomegalovirus (CMV) infection (trial CMX001-201; ClinicalTrials.gov identifier, NCT00942305). He received 200 mg of brincidofovir per week for 10 weeks. While enrolled in the study, BK viremia and viruria were monitored through week 24 post–HSC transplantation; the patient had persistent asymptomatic BK viruria, and BK viremia was undetectable with the exception of transiently low levels on 2 occasions. CMV viremia resolved at 12 months posttransplantation. The patient never developed Epstein-Barr or adenovirus viremia.

Approximately 6 months after transplantation, the patient experienced a relapse, which was treated with chemotherapy, donor leukocyte infusion, and lenalidomide. Approximately 10 months posttransplantation, he developed grade IV steroid-refractory acute graft-versus-host disease (GVHD) involving the gut and skin, which was treated with alemtuzumab and mycophenolate mofetil. Steroid dosage was tapered 15 months after transplantation. At 16 months, the patient developed acute kidney injury (Fig 1[17]). A kidney biopsy was performed, revealing PVAN with severe BK virus–associated tubulointerstitial nephritis with diffuse interstitial inflammation, multifocal tubulitis, acute tubular injury, moderate tubular atrophy, and interstitial fibrosis. Immunostaining showed abundant SV40 large T-antigen–positive tubular cell nuclei involving 25% to 35% of cortical and medullary tubules sampled; adenovirus and CMV antigens were undetectable. The vast majority of infiltrating lymphocytes were CD3+ T cells.

On day 572, based on biopsy-proven PVAN, the patient was enrolled in study CMX001-350, an open-label expanded-access study of brincidofovir in patients with serious diseases or conditions caused by infections with double-stranded DNA viruses (ClinicalTrials.gov identifier, NCT01143181). Brincidofovir was started orally at 100 mg twice weekly for 6 months. Figure 1 shows the patient's plasma BK viral load and estimated glomerular filtration rate during treatment.

No drug-related adverse events occurred. Following completion of CMX001-350, the patient continued treatment with brincidofovir under emergency investigational drug application provisions for an additional 5 months until he died of bacterial sepsis 30 months post–HSC transplantation. During this time, he had stable kidney function and did not require dialysis. No repeat kidney biopsy or autopsy was performed to directly document improvement in PVAN on a tissue level. The clinical course and immunosuppressive regimen of patient 1 are described in Box 1.

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