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The Pharmacologic Treatment of Human Polyomavirus Infection

Julie Roskopf, William Fitzsimmons, Nasimul Ahsan, and David Laskow

Human polyomavirus (PV) infections are increasingly being recognized as a cause of significant morbidity and mortality in a subset of patients. Patients at highest risk for developing clinically significant disease due to polyomavirus include recipients of organ transplants and patients with human immunodeficiency virus type 1 (HIV-1) infection, due to impaired cellular immunity. BK virus (BKV) is most frequently associated with nephropathy and ureteral stenosis in renal transplant patients and nonhemorrhagic and hemorrhagic cystitis (HC) found predominantly in bone marrow transplant recipients. JC virus (JCV) is known to cause progressive multifocal leukoencephalopathy (PML) and is most commonly seen in patients who have HIV-1 infection. The treatment strategy for patients, regardless of the type of polyomavirus, is the judicious lowering of immunosuppression or the treatment of the underlying immunodeficiency disorder. In addition, patients may benefit from antiviral agents with activity against polyomaviruses. Cidofovir has been used successfully to treat patients with BKV-induced transplant nephropathy or BKV-induced HC. The nucleoside analogue vidarabine has also been used to treat BKV-induced HC. A different nucleoside analogue (cytarabine), interferons, highly active antiretroviral therapy (HAART), cidofovir, and the topoisomerase I inhibitors have all been used to treat AIDS-associated PML with variable success. Several other compounds, including retinoic acid and the malononitrilamide compound FK-778, may also prove to be useful antipolyomavirus compounds. It is clear that the optimal management of patients with polyomavirus infections is still unclear, but further research is ongoing and is likely to improve the care we are able to provide these patients.

Introduction

Polyomavirus (PV) is a nonenveloped, double-stranded deoxyribonucleic acid (DNA) virus that is a member of the Polyomaviridae family.² Human PV infections are due to BKV and JCV. Clinically significant disease due to PV is primarily found in patients with impaired cellular immunity such as recipients of organ transplants or patients with HIV-1 infection and is linked to the degree of overall immunosuppression.²³

BKV

BKV is most frequently associated with nephropathy (interstitial nephritis) and ureteral stenosis in renal transplant recipients, as well as nonhemorrhagic and hemorrhagic cystitis (HC), found predominantly in bone marrow transplant recipients.³⁴ Clinical disease with BKV manifests principally in the genitourinary tract because the virus is known to remain latent in the kidney.³ There is currently no standardized treatment available for patients diagnosed with BKV-associated disease. The most common treatment strategy is to drastically reduce or discontinue immunosuppressive drugs and treatments, if possible. This approach is designed to reduce viral replication but may be associated with risks such as acute rejection and graft loss in renal transplant patients, and patients must be monitored closely.³⁴

BKV-Induced Transplant Nephropathy

Certain risk factors, such as multiple acute rejection episodes and the availability of more potent immunosuppressive medications, have been associ-
ated with BKV nephropathy (typically, interstitial nephritis).\textsuperscript{7} Patients often present with a rise in serum creatinine, necessitating further investigation. The diagnosis requires biopsy of the allograft and the use of either immunohistochemical analysis or in situ hybridization. These advanced techniques are needed to help distinguish if the tubular injury is due to the virus or the presence of concurrent acute rejection.\textsuperscript{7}

A better understanding of how to manage BKV-induced nephropathy is slowly evolving. Historically, it was difficult to exclude concurrent acute rejection on biopsy; therefore, many patients were given intensified immunosuppressive regimens to treat acute rejection. This resulted in graft loss in a large number of patients, likely due to BKV (Table 1). Some authors have suggested that if subclinical acute rejection is found concomitantly on tissue biopsy, these patients may benefit from pulse steroid therapy followed by a reduction in baseline immunosuppression.\textsuperscript{2,14} Although steroids may be of benefit, other authors have suggested it is best to avoid anti–T-cell agents such as OKT-3 and antithymocyte globulins after a diagnosis of BKV nephropathy has been made.\textsuperscript{7,13}

Better diagnostic testing and more experience suggest that in the case of BKV nephropathy the mainstay of therapy is to lower the amount of maintenance immunosuppression so that the patient can overcome the viral infection.\textsuperscript{6,7,9,13} Several approaches have included reducing or stopping azathioprine, mycophenolate mofetil, or sirolimus; using lower target concentrations of the calcineurin inhibitors (cyclosporine or tacrolimus); switching from one calcineurin inhibitor to another; or stopping the calcineurin inhibitor completely. This has resulted in a variety of different outcomes (Table 1). Cidofovir (HPMPC: (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine) is an acyclic nucleoside phosphonate that is active against virtually all herpesviruses, as well as papovaviruses (polyomaviruses and papillomaviruses), adenoviruses, iridoviruses, and poxviruses (Fig. 1). Andrei and colleagues evaluated several different antiviral compounds, and cidofovir was found to be the most selective inhibitor of murine polyomavirus.\textsuperscript{20} The spectrum of activity for cidofovir is very different from classic acyclic nucleoside analogues such as acyclovir, penciclovir, and ganciclovir. In murine models, cidofovir is more effective than acyclovir against herpes simplex virus (HSV) infection and more effective than ganciclovir against cytomegalovirus (CMV) infection.\textsuperscript{21,22} The active intracellular metabolite, cidofovir diphosphate, suppresses viral replication by the selective inhibition of viral DNA synthesis.\textsuperscript{23} Cidofovir diphosphate accumulates in the cell (half-life = 65 h) and allows for a long-lasting antiviral effect with infrequent dosing. Cidofovir is currently approved for CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). It is often reserved for patients who are unresponsive to or have relapsed on intravenous ganciclovir or foscarinet.\textsuperscript{22,24}

Recently, the successful use of cidofovir in 12 patients with BKV nephropathy has been described.\textsuperscript{25} Cidofovir was administered as a single dose of 0.25 to 1 mg/kg every 2 to 3 weeks intravenously (IV) for a total of 1 to 4 doses. Low doses (5%–20% of the dose recommended for the treatment of CMV retinitis, given less often) were used because the...
### Table 1 | Outcomes of Various Management Strategies in Patients with Posttransplant BKV Nephropathy

<table>
<thead>
<tr>
<th>Source</th>
<th>Disease Onset (Months)</th>
<th>Patient Number</th>
<th>Pharmacologic Management</th>
<th>Outcome/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathur et al.</td>
<td>Mean = 9.3 ± 4.3</td>
<td>7</td>
<td>1 patient: Given antirejection therapy</td>
<td>Diagnosed at nephrectomy</td>
</tr>
<tr>
<td>Randhawa et al.</td>
<td>Mean = 9.6 ± 13</td>
<td>11</td>
<td>1 patient: Decrease IS</td>
<td>Diagnosed at nephrectomy</td>
</tr>
<tr>
<td>Howell et al.</td>
<td>Mean = 9.6 ± 13</td>
<td>11</td>
<td>1 patient: Decrease IS</td>
<td>Diagnosed at nephrectomy</td>
</tr>
<tr>
<td>Nickeleit et al.</td>
<td>Mean = 9.3 ± 4.3</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Ahuja et al.</td>
<td>Median = 9.5 ± 6.2</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Barri et al.</td>
<td>Mean = 9.6 ± 13.5</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Mayr et al.</td>
<td>Mean = 9.6 ± 13.5</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Hirsch et al.</td>
<td>Mean = 9.6 ± 13.5</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Hussain et al.</td>
<td>Median = 9.5 ± 6.2</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Scantlebury et al.</td>
<td>Mean = 9.6 ± 13.5</td>
<td>10</td>
<td>10 patients: Given antirejection therapy and later decrease IS</td>
<td>7/10 graft failure (6 rapid)</td>
</tr>
<tr>
<td>Guardia et al.</td>
<td>Not reported</td>
<td>8</td>
<td>8 patients: Decrease IS</td>
<td>3/6 had 1 or more AR episodes</td>
</tr>
<tr>
<td>Trole et al.</td>
<td>Kidney: Median = 9.6</td>
<td>10</td>
<td>10 patients: Decrease IS</td>
<td>1/10 developed mild steroid sensitive AR</td>
</tr>
<tr>
<td>Ramos et al.</td>
<td>Mean = 12.8 ± 4.3</td>
<td>67</td>
<td>52 patients: Decrease IS</td>
<td>8/52 (15.3%) developed AR</td>
</tr>
</tbody>
</table>

IS, immunosuppression; AR, acute rejection; HD, hemodialysis.
majority of cidofovir (75%–80%) is excreted unchanged in the kidney, and the goal is to treat virus localized in the kidney. Using quantitative polymerase chain reaction (PCR) for BKV, all patients showed clearance of viremia and either clearance or significant reduction of viruria. No lasting nephrotoxicity was seen with low-dose cidofovir, and the serum creatinine improved in all patients after treatment. Several patients have had recurrence of the viruria; therefore, after treatment, patients still need to be monitored closely. Vats suggests that quantitative PCR testing can be used to diagnose and manage the course of BKV nephropathy and that cidofovir therapy may be beneficial in select patients, especially those who have not responded to a reduction in immunosuppression.

The most common clinical adverse events reported, when cidofovir is used to treat CMV retinitis, include nephrotoxicity (specifically proteinuria), nausea and vomiting, and fever. Cidofovir has also been associated with neutropenia and intraocular inflammation (uveitis). To minimize the risk of nephrotoxicity when treating CMV retinitis, cidofovir is routinely given with high-dose oral probenecid (used to block the uptake of cidofovir by the proximal tubular cells) and saline prehydration (at least one liter of sodium chloride 0.9%) with each dose. When cidofovir is used to treat BKV nephropathy, however, lower doses of cidofovir are used (as mentioned above). This helps to minimize the risk for developing adverse events such as dose-dependent nephrotoxicity. Probenecid has been used in patients being treated for BKV nephropathy, to allow for maximal excretion of the drug by the kidney, but prehydration with normal saline is still recommended. A second liter of fluid may be given over 1 to 3 hours during or after the cidofovir infusion if the patient will tolerate it.

Mayr and colleagues have devised an algorithm for the screening, diagnosis, and monitoring of patients with BKV nephropathy. This algorithm includes the use of urine cytology to screen for decaying cells in high-risk patients. If there are > 5 decaying cells per 10 high-power fields found repeatedly, a plasma PCR to check for BKV is done. If this is repeatedly positive, then an allograft biopsy is done. If the diagnosis of BKV nephropathy is made, overall immunosuppression is decreased. If acute rejection is also present on the biopsy, the authors recommend the use of pulse steroids to treat the acute rejection, followed by a reduction in immunosuppression. We have devised an algorithm for the pharmacologic management of BKV nephropathy (Fig. 2). Many authors support the reduction or discontinuation of the antimetabolic agent in addition to reducing the target concentrations of the calcineurin inhibitor. Cidofovir should be considered for patients who have persistent viremia/viruria despite a reduction in immunosuppression, especially if their renal function continues to worsen. Further research is needed to delineate if using this type of approach to treat BKV nephropathy is optimal to minimize progressive deterioration of renal function and ultimately prevent graft loss.

BKV-Induced HC

HC is a well-defined complication following treatment with high-dose cyclophosphamide often used in bone marrow or stem cell transplant patients, and it typically occurs within 48 hours of infusion. HC associated with BKV differs because it most commonly occurs late and is long lasting. Despite the cause of HC, treatment is largely supportive and often includes hydration, alkalization of the urine, bladder irrigation, pain management, antibiotics, and maintaining adequate platelet
The intravesical installation of drugs such as formalin, aluminum, silver nitrate, and prostaglandin E2 (PGE2) may also be used for more severe HC requiring more aggressive treatment, but bladder spasms tend to occur in most patients and may limit its usefulness.11,21

When cidofovir is used to treat BKV nephropathy, low doses of cidofovir are used to help minimize the risk for developing adverse events such as dose-dependent nephrotoxicity.
Several different drugs have been used to treat BKV-associated HC found in patients after either allogeneic bone marrow or stem cell transplant. The nucleoside analogue vidarabine (adenine arabinoside or Ara-A) is known to be active against several double-stranded DNA viruses.\(^{33}\) It appears to exert its antiviral effects by interfering with the early steps in viral DNA synthesis.\(^{33}\) Ara-A use has been described in several case reports. Chapman et al.\(^{29}\) successfully treated a 23-year-old man with BKV-associated HC with Ara-A 10 mg/kg/day for 5 days, given IV over 12 h. Within 2 days, his symptoms improved, after 7 days he was symptom free, and within 20 days the virus was cleared from the urine. In another case series, Ara-A (10 mg/kg/day for 5 days, given IV over 2.3 h) was used in 1 patient with polyomavirus-associated cystitis and in 2 patients with asymptomatic polyoma viruria. With Ara-A therapy, the viral inclusion bodies in urinary sediments disappeared in all 3 patients. In 1 patient, the viruria recurred and was successfully cleared with another course of Ara-A.\(^{33}\) In another case report, severe polyomavirus-associated HC was treated with Ara-A (10 mg/kg/day for 5 days, given intramuscularly), resulting in resolution of HC within 24 h of starting therapy and clearance of the virus from the urine after 4 days of treatment. Intramuscular Ara-A may be an alternative when patients have an adequate platelet count but do not have IV access.\(^{30}\) The most common side effects of Ara-A include nausea, vomiting, diarrhea, increased liver function tests, headache, confusion, and tremor.\(^{33}\) In the case reports above, Ara-A was associated with fatigue, nausea, vomiting, diarrhea, claustrophobia, and a transient increase in liver function tests.\(^{33,29,34,35}\) Ara-A appears to be a safe and effective therapeutic alternative for BKV-associated HC, but parenteral Ara-A is no longer available in the United States. Ara-A was historically used to treat varicella-zoster and herpes simplex virus infections, but drugs such as acyclovir are now used to treat these types of viruses.\(^{33}\)

There are several case reports describing the use of cidofovir for BKV-associated HC.\(^{27,28,36}\) In 1 patient, after palliative treatment of HC failed, cidofovir was initiated at 5 mg/kg/week IV for 2 weeks, followed by 5 mg/kg IV every 2 weeks for a month (total 6 weeks) with concurrent probenecid to minimize the risk for nephrotoxicity. Symptoms improved after 2 weeks, and BK viruria cleared. The patient experienced nausea and vomiting thought to be secondary to probenecid and also a slight increase in serum creatinine that resolved in 1 week with IV hydration.\(^{37}\) A different patient who had CMV reactivation in addition to BKV-associated HC was treated with cidofovir. Cidofovir is known to have potent activity against CMV in addition to polyomaviruses. Cidofovir was given as a single 5 mg/kg infusion and was repeated at 1 week and 3 weeks. Probenecid and IV hydration were also given simultaneously. As the BK viruria improved, the patient’s symptoms of HC improved, and the CMV antigenemia also became negative. The serum creatinine became slightly elevated but returned to baseline.\(^{38}\) In another patient, cidofovir was used for BKV-associated HC, but treatment failed and the patient underwent cystectomy.\(^{28}\) It appears that cidofovir is safe and effective in this setting of BKV and should be considered for patients who fail conventional methods for controlling HC.

**JCV and PML**

JCV causes progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the central nervous system. PML is most commonly seen in patients who have HIV-1 infection, with the average survival after diagnosis ranging from approximately 2.5 to 4 months.\(^{37}\) Cases of PML have also been described in patients with lymphoproliferative disorders, inherited primary immunodeficiency diseases, and exposure to high-dose chemotherapy, as well as in patients on prolonged immunosuppressive therapy (i.e., renal, liver, and heart allograft recipients and patients with rheumatoid arthritis).\(^{39-40}\)

Currently, no effective therapy for PML has been clearly established, but progress has been made over the years due to a better understanding of the disease. The general treatment strategy is to minimize or discontinue immunosuppression, as described earlier in patients with BKV, or to try and correct the underlying immunodeficiency.

Historically, different drugs have been used to try and treat PML. The antiviral agent Ara-A has been used in an attempt to block JCV DNA replication.
In a case report by Rand et al.,\textsuperscript{32} Ara-A did not appear to provide any significant clinical benefit when used systemically for 2 patients with advanced PML. A different nucleoside analogue, cytarabine (cytosine arabinoside or Ara-C), has been used frequently to treat PML. The efficacy of Ara-C has been supported by some uncontrolled studies but not by others.\textsuperscript{33-36} Based on in vitro data showing that Ara-C could block JCV DNA replication without overt toxicity to glial cells, Ara-C was studied more formally.\textsuperscript{37} The AIDS Clinical Trials Group (ACTG) Study 243 was a multicenter, open-label trial that was conducted to evaluate the use of Ara-C in HIV-infected patients with biopsy-confirmed PML.\textsuperscript{37} The study was designed to enroll 90 patients, but only 64 patients were enrolled, and 57 patients were evaluated. Patients were randomly assigned to one of three treatment groups, each lasting 24 weeks (Fig. 3).

Twenty-two patients (39\%) died during the study, and only 7 patients (12\%) completed the 24-week study. The study closed early after 24 months, after finding that there was no statistical difference in the survival rates between the three treatment groups ($p = 0.85$). The major toxicity associated with Ara-C therapy was hematologic (lower hemoglobin and platelet counts), and it occurred more often in the intravenous Ara-C group. More recently, Levy et al.\textsuperscript{43} have suggested that Ara-C failure in the ACTG Trial 243 was due to inadequate drug delivery to target cells in the brain. They have proposed that alternative methods used to infuse Ara-C directly into the brain may prove efficacious.

Early reports also describe the use of interferons that possess antiviral and immunomodulating activity. Tashiro and coauthors\textsuperscript{44} reported the use of intrathecal beta-interferon in a single patient that resulted in stabilization of her neurological status. More recently, Huang and colleagues\textsuperscript{45} reported results of an open-label study in HIV-associated PML patients. Untreated patients ($n = 32$) were compared to patients ($n = 21$) who received alpha-interferon (3 weeks minimum of either 3 million units SCQ every day or 5 million units SQ three times per week). The median survival time was significantly prolonged in treated patients (325 days) versus untreated patients (121 days) ($p < 0.001$). Side effects in the treatment group occurred in 19\% of patients and included leukopenia, pancytopenia, depression, and fatigue. The authors concluded that alpha-interferon should be studied more formally in a randomized clinical trial.

Improved survival has been reported for PML patients who receive highly active antiretroviral therapy (HAART).\textsuperscript{46,47} This therapy is designed to achieve an undetectable HIV ribonucleic acid (RNA) viral load and an increase in CD4 cell count and often correlates with a patient’s inherent ability to mount an immune response. HAART has emerged as an essential component of treatment for patients with PML; however, reports of PML exist in patients who are maximized on HAART therapy, and worsening of PML (both clinically and radiologically) has been reported in patients upon the initiation of HAART, suggesting an inflammatory reaction had occurred.\textsuperscript{48,49} In fact, despite HAART, the incidence of PML has been relatively constant.\textsuperscript{50} This has underscored the importance of identifying antiviral medications that are effective against JCV because reversing immunosuppression is not enough to alter the morbidity and mortality associated with PML in all patients.\textsuperscript{51}

There have been numerous case reports describing the use of cidofovir for PML.\textsuperscript{24,52-56} A multicenter observational study was conducted to assess if HAART plus cidofovir therapy was more effective than HAART alone in patients with AIDS-related PML.\textsuperscript{57} Group A consisted of 27 patients treated with HAART alone, and group B consisted of 16 patients treated with HAART plus cidofovir. The probability of survival at 1 year was 0.29 in the HAART-alone group and 0.61 in the HAART-plus-cidofovir group ($p = 0.02$). Evaluation at 2 months revealed that 5 of 12 patients tested (42\%) in group A had undetectable JCV DNA in the cerebrospinal fluid (CSF), compared to 7 of 8 patients...
These compounds may add to the current armamentarium of agents used to treat polyomaviruses, and further research will aid in defining the optimal management for patients requiring treatment for clinically significant polyomavirus infections.

REFERENCES


