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Cidofovir in the Treatment of BK Virus–Associated Hemorrhagic Cystitis after Allogeneic Hematopoietic Stem Cell Transplantation

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A B S T R A C T

After allogeneic hematopoietic stem cell transplantation (HSCT), BK virus–associated hemorrhagic cystitis (BKV-HC) is a common complication. Although supportive measures have been the standard of care for many years, several studies suggested the efficacy of cidofovir. The aim of this study was to assess the safety profile and efficacy of cidofovir. A retrospective study was conducted on all patients treated with cidofovir in our HSCT unit between March 2011 and May 2013. Data for efficacy (partial [PR] or complete response [CR]), prescription (dose, frequency, number of doses, and administration route), and toxicity were collected from published reports and medical files. Renal toxicity was evaluated using creatinine clearance calculated with the Cockcroft and Gault formula. A parallel literature search using PubMed (last search, May 2015) was performed. From March 2011 to June 2013, 27 of 181 patients undergoing allogeneic HSCT in our department received cidofovir for BKV-HC: 24 (88.9%) intravenously, 1 intravesically, and 2 via both routes. Mean dose was 5 mg/kg per administration, for a median of 4 injections (range, 1 to 11), from twice a week to once every 2 weeks. CR was achieved in 22 patients (81.5%), PR in 2, and no response in 2 patients. Eight patients presented renal failure (29.6%): 6 moderate (creatinine clearance $<$ 60 mL/min) and 2 severe (creatinine clearance $<$ 30 mLmin). Mean decrease in creatinine clearance after cidofovir was 27% (35 mL/min; range, 2 to 159). In 3 cases renal insufficiency and hematologic toxicity led to discontinuation of treatment or switch to intravesical instillation. For 3 patients cidofovir dose was reduced because of nephrotoxicity. Thirteen studies have reported on the use of cidofovir for BKV-HC (204 patients) since 2005. Intravenous cidofovir was used for 91.3% of patients, with doses ranging from .5 to 5 mg/kg. The main toxicity reported was renal failure (9% to 50% in 9 studies). Between 60% and 100% of CRs were observed independently of cidofovir dose or administration route. Cidofovir is an effective therapy for BKV-HC but requires very precise renal function management to avoid toxicity. Cidofovir treatment modalities (high dose, intravesical instillation, or low dose [$\leq$1 mg/kg]) needs to be investigated in randomized controlled trials.

INTRODUCTION

BK virus–associated hemorrhagic cystitis (BKV-HC) is a common complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1], with an incidence ranging from 7% to 70% in various reports [2,3]. HC may cause significant morbidity and prolonged hospital stays, with severe hematuria (grades 3 or 4) in 8% to 27% of allo-HSCT

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patients [4]. Although its pathogenesis is not yet clearly elucidated, it is associated with factors related to transplant procedure (eg, myeloablative conditioning regimen), onset of acute graft-versus-host disease and high-level urinary BKV replication, and the graft source (unrelated donor, cord blood unit transplantation, HLA mismatching) [4-6]. Indeed, HC is more prevalent in matched unrelated donors and unrelated cord blood transplantation than in matched related donor transplantation [7,8]. In addition to HC, BKV is also incriminated in nephropathy in kidney transplantation [9] and more rarely in fatal pneumonia, native kidney nephritis, and encephalitis in severely immunocompromised patients [10]. BKV is a nonencapsulated DNA human polyomavirus with high prevalence in healthy adults, with up to 90% seropositivity [10]. Transmission is believed to occur via the respiratory tract, especially during early childhood. Infection is usually asymptomatic or may be associated with fever and mild upper respiratory symptoms [2,11]. After the first infestation polyomavirus can be latent in the kidneys, urothelium, and other organs and may be reactivated during immunosuppression. In allo-HSCT patients immune suppression related to aplasia or treatment to prevent graft rejection and/or prophylaxis of graft-versus-host disease likely favor BKV reactivation.

Supportive measures (bladder irrigation, blood transfusion, and symptom relief) have been the standard of care for many years for this difficult-to-treat complication, and many alternative treatments have been tried (ganciclovir, leflunomide, long-term ciprofloxacin, hyperbaric oxygen therapy) [1,12]. To date, no antiviral drug with proven efficacy against BKV replication has been licensed, but some case series and case reports have suggested some efficacy for cidofovir in the treatment of BKV-HC [4,13-15].

Cidofovir is a nucleotide analog of cytosine that is active against various DNA viruses and was approved as an intravenous treatment for cytomegalovirus retinitis in AIDS patients. In vitro, it is active against a broad spectrum of herpes viruses (cytomegalovirus, herpes simplex types 1 and 2, varicella-zoster virus, Epstein-Barr virus, and human herpesvirus types 6 and 8) and human papillomavirus and adenovirus [16-18]. Impaired renal function (creatinine clearance $<$ 55 mL/min or proteinuria $\geq$ 2+) is the main contraindication, particularly in case of concomitant administration of nephrotoxic agents. The nephrotoxicity of cidofovir is dose dependent, with proximal tubular cell injury and elevation of serum creatinine. Adding probenecid to cidofovir is recommended to keep a sufficient plasma concentration to allow once-a-week administration [19]. Probenecid decreases the intratubular penetration and accumulation of cidofovir in kidney cells by inhibiting tubular secretion [20]. Many case reports have shown that cidofovir could be a very interesting alternative in BKV-HC, but it is not licensed for this indication and is currently difficult to use because of a recent global disruption. The aim of the present retrospective study was to assess the safety profile and efficacy of cidofovir in allo-HSCT patient, associated with a literature review.

METHODS

Retrospective Study

All patients who received at least 1 dose of cidofovir in our HSCT unit between March 2011 and June 2013 were identified on the pharmaceutical software used to prepare injectable drugs (Asclepios). BKV-HC was diagnosed on clinical and biological criteria: association of hematuria and positive BKV viruria and/or viremia. BKV detection in urine and plasma samples has been measured by PCR, as follows: DNA was extracted by an automatic nucleic acid platform (Nuclisens EasyMag; Biomerieux). BKV DNA quantification was carried out by BKV R-GeneTM (bioMerieux–Argene) using the ABI Prism 7500 Real Time PCR System (Applied Biosystems).

Severity was graded following Bedi et al. [21]: grade 1, microscopic hematuria on more than 2 consecutive days; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with clots; and grade 4, macroscopic hematuria with clots and impaired renal function secondary to tract obstruction. The following data were collected from the pharmaceutical software: dose, number of injections, treatment duration, cumulative dose, and cidofovir administration route. Clinical efficacy and cidofovir-related toxicity were collected from medical files. Clinical efficacy was assessed at the end of cidofovir treatment as a complete clinical response for full symptom remission, partial clinical response for downgrading of BKV-HC severity, or clinical failure for unchanged or worsened clinical status. Renal toxicity was assessed by creatinine clearance estimated by the Cockcroft and Gault formula, before the first dose and after the last dose of cidofovir.

Literature Review

A literature search was conducted using PubMed (last search, May 2015). The following keywords were used: “cidofovir” plus “hemorrhagic cystitis,” “polyomavirus,” and “BK virus.” Limits were set to include human subjects (children or adults) with BKV-HC after allo-HSCT. The following information was collected and double-checked by 2 investigators: efficacy in terms of partial (PR) or complete response (CR), cidofovir prescription modalities (dose, frequency, number of doses, and administration route) and reported toxicity.

RESULTS

Retrospective Study

Patients

In total, 27 patients (12 women, 15 men) treated with cidofovir were included. Patient and donor characteristics and conditioning regimens are detailed in Table 1. Mean age was 42 years (range, 21 to 60). All patients were treated for BKV-HC after allo-HSCT. One patient had concomitant reactivation of adenovirus in blood. The underlying diseases were acute myeloid leukemia (n = 17), acute lymphoblastic leukemia (n = 3), non-Hodgkin lymphoma (n = 2), myelodysplastic syndrome (n = 2), chronic lymphocytic leukemia (n = 1), aplastic anemia (n = 1), or primary myelofibrosis (n = 1).

Median interval between HSCT and BKV-HC onset was 63 days (range, 14 to 189). Clinical HC severity was grade 1 in 8 patients (29.6%), grade 2 in 13 (48.2%), grade 3 in 3 (11.1%), and grade 4 in 3 (11.1%). At diagnosis, BK viremia was positive in 25 patients (92.6%), negative in 1 (3.7%), and not investigated in 1 patient (3.7%). BK viruria was positive for all patients except 1, in whom it was not investigated because associated viremia was highlighted.

Dosing

Data relating to cidofovir treatment, efficacy and tolerance are summarized in Tables 2 and 3. Except supportive measures (bladder irrigation, blood transfusion, and symptom relief), no patient received any other treatment for BKV-HC before the use of cidofovir. Twenty-four patients were treated intravenously, 1 by intravesical instillation (patient 26), and 2 patients via both administration routes separately (patients 21 and 22). All patients receiving intravenous cidofovir were given oral probenecid: 2 g 3 hours before and 1 g 3 hours and 9 hours after cidofovir administration. Intravenous hydration with normal saline was also given. Regardless of administration route, median cidofovir dose was 5 mg/kg per administration, median cumulative dose was 16.3 mg/kg per patient (range, 5 to 67 mg/kg), and median number of injections was 4 (range, 1 to 11). Depending on HC severity and treatment tolerance, rate of administration ranged from twice a week to once every 2 weeks; mostly, administration was once a week for 2 weeks and then 2 injections at 2-week intervals.