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Original article

Endovesical instillation of Cidofovir in the treatment of BK polyomavirus hemorrhagic cystitis after allogeneic hematopoietic cell transplantation

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ABSTRACT

Background: Hemorrhagic cystitis (HC) with BK polyomavirus (BKPyV) is a common complication after allogeneic hematopoietic cell transplantation (alloHCT) that may lead to severe discomfort for the patient and significant morbidity (urinary obstruction, increased transfusion requirements and prolonged hospitalization). So far, there is no clear consensus on how to manage this complication.
Patients and methods: Here, we report a single-center case series of 9 patients (4 children and 5 adults) treated with cidofovir endovesical (EV) instillation(s) for BKPyV-HC after alloHCT. EV Cidofovir was administered at a dose of 5 mg/kg, for 1 to 3 instillations (with a minimum delay between 2 successive doses of 5 days).
Results: Eight out of the 9 treated patients with EV Cidofovir achieved a complete resolution of HC after 1–3 instillation(s), without recurrence of symptomatic infection within the next 3 months. Only 1 adult patient did not improve after treatment and developed severe morbidity (emphysematous cystitis).
Conclusion: Although this single-center case series of EV cidofovir for BKPyV HC after alloHCT shows encouraging results, only large prospective studies will definitively establish the effectiveness of this therapy.

Introduction

BK polyomavirus (BKPyV)- associated hemorrhagic cystitis (HC) is a common complication after allogeneic hematopoietic cell transplantation (alloHCT). Risk factors include myeloablative conditioning regimen, alternative graft/donor source (cord blood, HLA-mismatched donor) and *in-vivo* T-cell depletion (with pre-transplant anti-T cell globulin or post-transplant cyclophosphamide). [1–6] More specifically, HLA-haploidentical donor alloHCT with post-transplant cyclophosphamide has been reported to be associated with a higher risk of BKPyV-HC. [1–3,5,6] Severe acute graft-versus-host disease (GVHD) and infection with cytomegalovirus (CMV) or human herpes virus type 6 (HHV-6) reflecting the immunosuppressive status are other known risk factors. [1–6]

BKPyV HC usually occurs at the time of neutrophil engraftment, but can be observed 2 weeks to 6 months after alloHCT. Its pathogenesis is thought to be a multi-step process: (1) subclinical lesions of the bladder mucosa caused by the conditioning regimen; (2) high-level BKPyV replication due to impaired antiviral immunosurveillance, leading to viral cytopathic effects on the urothelium; and (3) secondary inflammatory responses and invasion by donor-derived immune cells that induce further tissue damages. [2,7]

BKPyV HC may lead to severe discomfort for the patient, significant morbidity (urinary obstruction, increased transfusion needs, renal failure, prolonged hospitalization) and increased medical costs. [8] Concerns have also been raised about a detrimental impact of BKPyV HC on post-transplant survival, although this remains controversial. [4,8–10]

Currently, there is no consensus on how to manage BKPyV HC after alloHCT. Fluoroquinolones interfere with viral replication in vitro, but their use in the clinic is commonly discouraged based on limited evidence of clinical efficacy and the risk of promoting the emergence of multidrug-resistant bacteria. [11,12] Cidofovir is a cytosine nucleoside analogue that inhibits viral DNA polymerase. A few

Abbreviations: BKPyV, BK polyomavirus; HC, hemorrhagic cystitis; AlloHCT, Allogeneic hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CMV, cytomegalovirus; HHV-6, human herpes virus type 6; IV, intravenous; EV, endovesical

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studies have reported potential efficacy of intravenous (IV) cidofovir for controlling BKPyV HC but with risks of renal toxicity. [13–16] Cidofovir endovesical (EV) instillation(s) has shown safety but variable efficacy in small case series. [13–15,17–21] Hence, continuing to report real-life clinical outcomes with this therapy is important. Here, we report our single-center experience with 9 patients treated with EV cidofovir for BKPyV-HC after alloHCT.

Patients and methods

This is a single-center retrospective case-series analysis of pediatric and adult patients treated with EV cidofovir for BKPyV HC after alloHCT. Patients were transplanted between 07/2016 and 06/2020. The diagnostic of BKPyV HC was based on the following criteria: (a) clinical symptoms/signs of cystitis; (b) macroscopic hematuria; (c) BKPyV viruria > 7 $\log_{10}$ copies (cp)/mL and (d) exclusion of any other urinary co-infection. [2,5] The severity of hematuria was graded as commonly described: microscopic (grade I); macroscopic (grade II); macroscopic with clots (grade III); or macroscopic with clots and postrenal failure secondary to urinary tract obstruction (grade IV). [2] BKPyV viruria was quantified by a homemade RT-PCR for the detection of BK and JC polyomaviruses with a quantification threshold of 500 cp/mL (2,7 log/mL).

Based on our institutional protocol, EV cidofovir was considered for patients with a prolonged, very uncomfortable or complicated grade II-IV BKPyV HC (defined as HC requiring prolonged irrigation, endoscopic clot removal, prolonged hospitalization or patient with severe thrombocytopenia requiring high transfusion support). EV cidofovir was administered at a dose of 5 mg/kg (diluted in 50 ml NaCl 0,9% in sterile conditions), for 1 to 3 instillations (with a minimum delay between 2 successive doses of 5 days). The number of doses administered was left to the discretion of the attending physician. Instillations were performed through a urinary catheter and cidofovir suspension was maintained endovesically for 60 min (clamped catheter). In the case of grade III-IV HC, preliminary bladder irrigation and evacuation of the clots were carried out before initiating EV cidofovir. In children or in cases of known significant discomfort or bladder instability during previous administrations, a short sedation was administered. In addition to treatment with EV cidofovir, all patients received standard supportive care for HC (such as hyperhydration, bladder catheterization, bladder irrigation, transfusion and analgesia, all tailored to each specific situation). No patient received IV cidofovir. Serum creatinine was monitored during the first 2 weeks after each EV Cidofovir instillation. Acute kidney dysfunction after EV cidofovir was retrospectively assessed according to AKIN stadification system.

This retrospective analysis was performed in accordance with the ethical recommendations of the statement of Helsinki. All patients provided written informed consent for use of protected health data for research and this study was approved by our institutional committee.

Results

Patient characteristics are described in **Table 1**. Median age was 27 years (7- 53, with 4 children). The majority of patients was transplanted for non-malignant disorders, after myeloablative conditioning and with bone marrow grafts. Four patients were transplanted with an HLA-haploidentical donor. All of the 9 patients had received in vivo T-cell depletion with either pre-transplant anti-T cell globulin or post-transplant cyclophosphamide. In addition, 2 patients had acute GVHD and 1 patient CMV co-infection [22] treated with valganciclovir by the time of BKPyV HC. Six patients had grade IV thrombocytopenia with 2 of them being platelet transfusion-refractory and 1 patient had grade III thrombocytopenia (according to CTCAE grading scale).

HC characteristics and outcomes after EV cidofovir are detailed in **Table 2.** Median time between alloHCT and HC was 28 days (12 - 52) and median time from BKPyV HC diagnosis to first EV cidofovir was 20 days (6–77). Five patients had prolonged course of HC (evolving for at least 20 days) before first EV instillation of cidofovir. All patients had received prior therapy with fluoroquinolone (ciproxine BID) that was ineffective for controlling BKPyV HC. At the time of first EV cidofovir, 3 patients had grade II and 6 grade III HC. One patient received 1, 5 patients received 2 and 3 patients received 3 EV instillations. In patients treated with repeated administrations, the median delay between 2 successive EV instillations was 7 days (5 - 31).

Eight patients achieved a complete resolution of HC under this therapy: one patient after 1 dose (within 7 days after the instillation), 4 patients after 2 repeated doses (with an estimated delay ranging 8 to 14 days from the first instillation) and 3 patients after 3 repeated doses (with an estimated delay ranging 23 to 25 days from the first instillation). All but one of the patients with severe thrombocytopenia (6/7) achieved a complete resolution of HC under EV cidofovir therapy, with 4 of them within 2 weeks after the first EV instillation (3 after 7 - 8 days and 1 after 13 days). None of these 8 responders to EV cidofovir relapsed BKPyV HC within the 3 months post-treatment. Only one adult patient (patient 8) did not respond to EV cidofovir and developed severe morbidity (necrotizing cystitis, see below).

Viruria was monitored in 4 patients: 1 patient cleared viruria after 1 month, 2 responding patients maintained prolonged asymptomatic viruria and viruria persisted in the non-responding patient. Viremia and BKPyV-specific antibodies were not assessed in this cohort.

A total of 20 EV cidofovir instillations were performed, 11 of which were administered under short sedation. Of the 9 instillations performed without sedation, 6 caused immediate bladder spasms and discomfort requiring antispasmodics and level 2 analgesics and/or early release of the clamp and/or short sedation for subsequent administrations. We did not observe significant increase of serum creatinine levels after EV Cidofovir in comparison with baseline renal function (according to AKIN stadification).

In patient 8, EV cidofovir failed to improve HC which progressed to grade IV hematuria and severe necrotizing cystitis requiring radical cystoprostatectomy (**Fig. 1**). This occurred after a prolonged and complicated course of HC (131 days since the diagnosis of BKPyV HC, requiring multiple bladder irrigations, endoscopic clot removal and permanent catheterization), in a highly comorbid patient (grade IV thrombocytopenia, severe acute GVHD requiring 4 lines of immunosuppressive therapy, diabetes mellitus, malnutrition) and after a secondary polymicrobial (Gram-negative bacilli) urinary superinfection. The patient had received 2 doses of EV cidofovir (with the second instillation being carried out 18 days before the onset of the complication). Histopathological examination revealed large mucosal ulcerations, transparietal hemorrhagic necrosis, no lymphoid cell infiltration and no signs of malignant transformation (**Fig. 1**).

Discussion

In this retrospective case-series of 9 patients (4 children and 5 adults) with BKPyV HC, we observed a good clinical response to EV cidofovir with resolution of the HC in 8/9 patients, without recurrence within the next 3 months. These results are in line with those reported in other case series [13–15,17,20,21] as well as in a systematic review (9 retrospective studies) that showed a 88% clinical response rate after EV cidofovir (N = 172) compared to 68% with IV cidofovir (N = 17). [15]

Among the eight responders to EV cidofovir, five patients achieved rapid (within 2 weeks) complete resolution of HC after 1–2 doses of EV cidofovir. These results have to be interpreted in the context that our cohort was represented by a majority of patients with prolonged prior course of HC (5 /9) and/or severe thrombocytopenia (7/9). The management of BKPyV HC in the setting of severe

Table 1.
Patients characteristics.

	Age (years)	Hematological disease	Conditioning regimen	Graft source, donor	CMV (D/R)	GVHD prophylaxis	Acute GVHD	CMV Co-infection	HHV6 Co-infection	Thrombo-cytopenia (CTCAE grade)
P1	34	AML	MAC	PBSC, haplo	-/+	Tacro/MMF/PTCy	No	No	No	Grade IV
P2	7	SCID	RIC	CB, UD	-/-	Tacro/MMF/ATG	No	No	No	Grade III
P3	15	B-thalassemia	MAC	CB + BM + PBSC, SIB	-/-	Tacro/MMF/ATG	No	No	No	No
P4	8	FA	RIC	BM, SIB	+/+	Tacro/MTX/ATG	No	No	No	Grade IV
P5	39	MLD	MAC	BM, UD	+/+	Tacro/MTX/ATG	No	Yes	No	No
P6	16	SAA	MAC	BM, UD	-/+	Tacro/MTX/ATG	No	No	No	Grade IV Tx-refractory
P7	53	AML	MAC	BM, haplo	-/+	Tacro/MMF/PTCy	No	No	No	Grade IV
P8	45	NHL	MAC	PBSC, haplo	-/+	Tacro/MMF/PTCy	Yes	No	No	Grade IV
P9	27	ALL	MAC	PBSC, haplo	+/+	Tacro/MMF/PTCy	Yes	No	No	Grade IV Tx-refractory

ALL indicates acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; ATG, anti-T cell globulin; BM, bone marrow; CB, umbilical cord blood; CMV (D/R), cytomegalovirus donor/recipient sero-status ; FA, Fanconi anemia; GVHD, graft-versus-host disease; Haplo, HLA-haploidentica donor; MAC, myeloablative conditioning; MLD, metachromatic leukodystrophy; MMF, mycophenolate mofetil; MTX, methotrexate; NHL, non-Hodgkin lymphoma; PBSC, peripheral blood stem cells; PTCy, post-transplant cyclophosphamide; RIC, reduced intensity conditioning; SAA, severe aplastic anemia; SCID = severe combined immune deficiency; SIB= 10/10 HLA-matched sibling donor ; Tacro = Tacrolimus ; Tx-refractory, platelet transfusion-refractory ; UD= unrelated donor.

Table 2.
BKPyV HC and outcomes after EV cidofovir.

	Time from alloHCT to HC (days)	Time from HC diagnosis to first EV cidofovir (days)	Grade of hematuria[1]	Viruria (log/mL)[1]	Number of EV cidofovir administered	Delay between 2 successive instillations, if multiple (days)	Resolution of HC	Time from the 1st (and subsequent) EV cidofovir to CR of HC (days)[2]	3-month recurrence of HC	Adverse events
P1	28	76	III	>7,7	2	7	Yes	8 (1)	No	Pain
P2	18	11	III	>7,7	2	7	Yes	8 (1)	No	N
P3	23	9	III	>7,7	3	7; 7	Yes	25 (18, 11)	No	Pain
P4	12	7	II	>7,7	3	7; 13	Yes	23 (16, 3)	No	N
P5	28	43	II	>7,7	2	9	Yes	14 (5)	No	Pain
P6	67	34	III	>7,7	3	5 ; 5	Yes	24 (19, 14)	No	N
P7	41	20	III	>7,7	1	N/A	Yes	7	No	N
P8	52	77	III	>7,7	2	31	No, evolution to grade IV HC	N/A	N/A	Transparietal necro-tizing cystitis
P9	45	6	II	>7,7	2	7	Yes	13 (6)	No	N

CR, complete resolution; N/A: not applicable (cystectomy).
[1] By the time of first EV cidofovir.

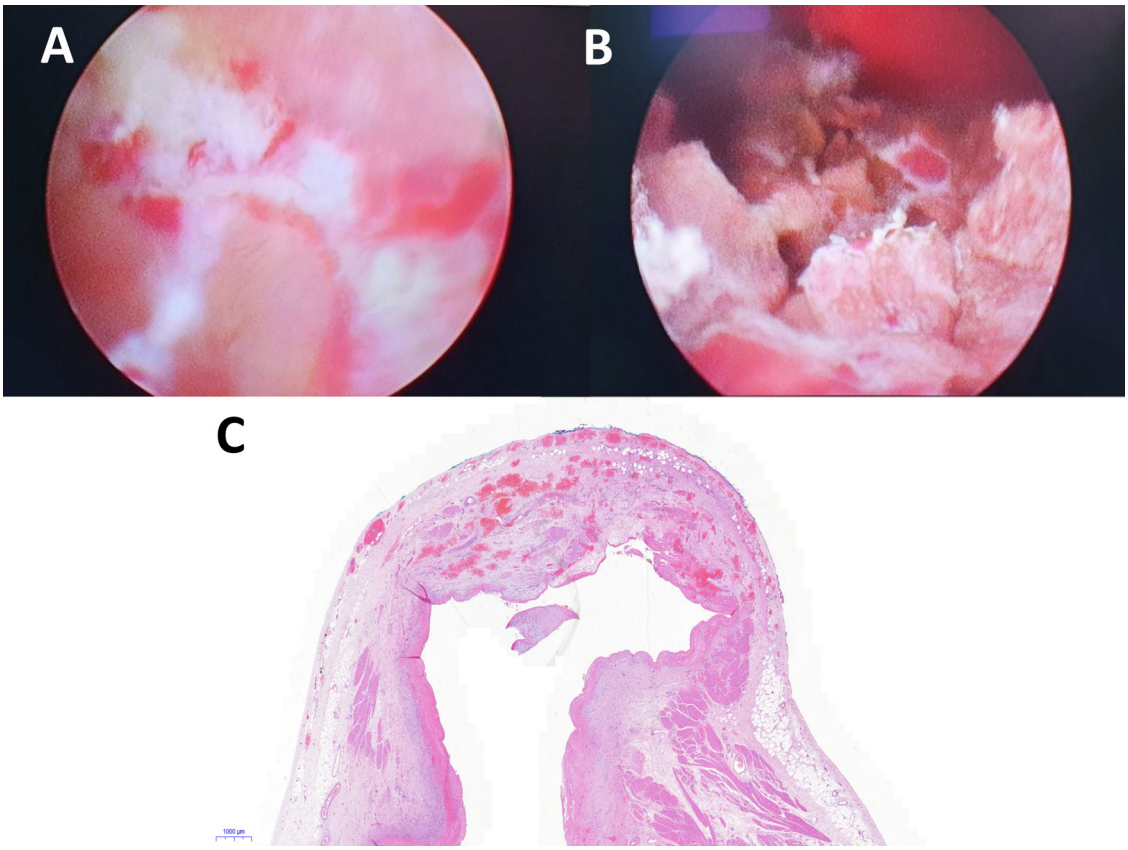

Fig. 1. Gangrenous cystitis (patient 8): (A, B) bladder endoscopy; (C) bladder histopathological examination after radical cystoprostatectomy

(A-B) Bladder endoscopic images revealed superficial (A) and profound (B) mucosal ulcerations with exposition of the detrusor muscle in some places (B); (C) Histopathology of the bladder showed transparietal necrosis, thinning of the bladder muscularis and multiple foci of intraparietal hemorrhage.

thrombocytopenia can be challenging (longer duration of HC, higher risk of grade III-IV HC, high requirement of transfusions, prolonged hospitalization). Hence, our results appear to be encouraging in terms of potential benefit of the strategy in a hardly manageable population of patients with severe thrombocytopenia and/or prolonged course of BKPyV HC.

Preservation of the renal function could be another substantial advantage of EV over IV cidofovir, with no acute renal failure observed in our cohort as well as in the systematic review (0% versus 9% with IV cidofovir). [15] However, few cases of acute nephrotoxicity have still been reported after cidofovir EV. [18,19] In a pharmacokinetic analysis in 6 adult patients with BKPyV or adenovirus HC, Aitken et al. reported that, compared with the reported AUC0−24 for an equivalent IV dose, EV instillation of cidofovir (given at a dose of 2.5 to 5 mg/kg over 30 to 120 min of clamp time) resulted in a 1% to 74% (median 4%) of the corresponding systemic exposure. [18] Thus, although the risk of renal insufficiency seems much lower with EV compared to IV administration, this risk is not completely zero and we recommend to monitor the renal function and to remain cautious, particularly in vulnerable patients with renal comorbidities or nephrotoxic co-medications.

Beyond antivirals, adoptive immunotherapy with anti-BKPyV-specific T-cells is currently explored in clinical trials and appears as a promising alternative for managing severe HC. [23,24] However, efficacy of such a therapy has to be balanced with risks of potential immune-mediated side effects (such GVHD, immune reconstitution syndrome, cytokine release syndrome) and elevated health care costs. [23,25]

The main adverse event of EV cidofovir in our patients was bladder spasms and/or pain. Such discomfort was similarly reported in about 30% of cases in other case series. [15] This could possibly be related to bladder spasms on the catheter or distention by the instilled volume but direct chemical mucosal irritation by cidofovir suspension is not formally excluded. In case of known significant discomfort or bladder instability during previous administrations or in children, short sedation may be useful. However, given the possibility of a spontaneous favorable course of BKPyV HC, the balance between the risks and benefits of cidofovir EV instillations must be carefully weighed. Our policy was to reserve this therapy for patients with a prolonged, very uncomfortable or complicated HC infection.

One highly immunosuppressed and comorbid adult patient failed to respond to EV cidofovir (2 instillations) and developed grade IV hematuria and severe emphysematous cystitis. The cause of this serious complication is likely multifactorial. Chronic irritation of the bladder mucosa by uncontroled BKPyV replication (profound immunosuppression), mechanical damages to the mucosa (bladder catheter), impaired hemostasis (severe thrombocytopenia) and limited tissue healing potency (corticosteroid therapy, protein malnutrition) might have contributed to the prolonged and severe course of HC in this fragile patient. Bacterial superinfection, urinary obstruction on clots and vesical distension may have further acted as aggravating factors in the progression to ischemia and transparietal necrosis. Stable immunosuppressive therapy and absence of lymphoid cell infiltrate within the tissues argue against worsening of bladder inflammation in the context of an immune reconstitution syndrome. Although this could not be formally excluded, it seems to us unlikely that EV cidofovir instillations could have been responsible for additional toxic effects since the delay of their administration from this complication and absence of previous warning information reported in pharmacovigilance. To the best of our knowledge, no other case of necrotic cystitis have been described after BKPyV infection or cidofovir IV or EV administration in alloHCT patients. It is very important to

continue to monitor the possible toxicities of this therapeutic approach. Our experience with this complicated case calls for caution when using EV cidovofir in vulnerable patients with a prolonged course of HC.

Limitations of this study stem from the retrospective nature of the analysis, the small cohort of patients, the absence of a control group and lack of information about viremia and anti-BKPyV-specific antibodies/T-cells. [26–28] Hence, in responding patients, the potential contribution of progressive immune reconstitution to HC resolution could not be apprehended.

Conclusion

Although this real-life single-center retrospective case series shows encouraging results with EV cidofovir for controling BKPyV HC after alloHCT, efficacy of such a therapy has to be confirmed in prospective trials as well as its precise safety profile.

Declaration of Competing Interest

None

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