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Internal Medicine Section

Real World Experience using Cidofovir in BK Polyomavirus Haemorrhagic Cystitis following Stem Cell Transplantation- Are Generics Equally Efficacious?

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ABSTRACT

Introduction: BK Polyomavirus induced Haemorrhagic Cystitis (BKPyV-HC), a well-recognised complication following Haematopoietic Cell Transplantation (HCT), is associated with increased organ dysfunction and mortality. The treatment is a multipronged strategy which includes manipulating immunosuppression and antiviral therapy along with newer advances of virus specific cellular therapy. Cidofovir is a nucleotide analogue of Cytosine that is effective against many Deoxyribonucleic Acid (DNA) viruses and its use has been limited in the past because of cost and toxicity.

Aim: To capture real world data on the use of cidofovir in BKPyV-HC, post HCT especially with regard to dosage, efficacy, toxicity and predictors of response to therapy. The study compared the efficacy and safety of the innovator molecule of cidofovir with Generic versions.

Materials and Methods: This study was a retrospective cohort of 67 patients, who were diagnosed with BKPyV-HC post haematopoietic stem cell transplant, and were treated with cidofovir. The study was conducted at a tertiary care centre at Vellore, Tamil Nadu, India, between 2015 and 2021. BKPyV Polymerase Chain Reaction (PCR) was checked in urine routinely in alternate donor transplants, and if there were typical lower urinary tract symptoms or haematuria in any other transplant setting. Treatment with cidofovir (initially innovator and subsequently generic) was as per physician's discretion. The descriptive data were reported as means with Standard Deviation (SD) or frequencies with percentages as appropriate.

Results: Total 985 patients underwent Allogeneic HCT during the study period, of which 67 had BKPyV-HC and were treated with cidofovir (47 with Innovator molecule, 20 with Generic molecule). There was clinical resolution in 47 (70.1%) and mortality in 32 (47.8%) of the cohort. On univariate analysis, risk factors associated with mortality were an absence of clinical resolution ($p<0.001$), treatment initiation at a higher grade of HC ($p=0.032$), CD34 cell dose $>9\times10^6$/Kg ($p=0.029$), partial remission of malignancy at the time of transplant ($p=0.001$), ≤3 doses of cidofovir used ($p=0.036$), BK log value >log 7 at the time of stopping cidofovir ($p=0.021$) and toxicity with cidofovir ($p=0.036$). However, only the absence of clinical resolution was significantly associated ($p<0.001$) with mortality risk on multivariate analysis. There was no significant difference between the two comparator molecules of cidofovir.

Conclusion: Cidofovir is an effective and safe therapeutic option to treat BKPyV-HC with no significant differences seen between the innovator and Generic molecule of Cidofovir in this small series of patients.

Keywords: Generic, Innovator, Stem cell transplant

INTRODUCTION

BK Polyoma Virus (BKPyV) is a double-stranded DNA virus belonging to the *Polyomaviridae* family. It was first isolated in 1971 from a renal transplant recipient with ureteric stenosis and was named after the initials of this patient [1]. It causes frequent infections during childhood and permanent latency of the virus in the uroepithelial and renal tubular cell but is of little significance in the immunocompetent host as more than 80% of adults are seropositive for BKPyV [2,3]. Reactivation of infection resulting in morbidity is observed in Human Immunodeficiency Virus (HIV) positive and transplant recipients. In HCT recipients, infection with BKPyV is mainly associated with HC with a reported incidence ranging from 7-40% depending on HCT type, population (8-25% of paediatric and 7-54% of adult recipients) and HC severity [4-7].

Treatment of BKPyH-HC is a four-pronged strategy consisting of a gradual reduction in immunosuppression, treatment with antivirals such as cidofovir, replacement of immunoglobulin until immune reconstitution and cellular immunotherapy with virus-specific T-cells [2]. Cidofovir, a nucleotide analogue of Cytosine that is effective against many DNA viruses, is approved to treat Cytomegalo Virus (CMV) retinitis in HIV seropositive patients [8]. In BKPyV, it has been shown to inhibit viral DNA replication downstream of large T-cell antigen expression [9]. The addition of probenecid decreases intratubular penetration and accumulation of cidofovir in the kidney and allows steady plasma concentration to enable dosing once a week [10]. Using cidofovir at doses from 0.5 mg/kg to 5mg/kg [8], intravenous or intravesical, has been shown to have response rates up to 70-100% [8,11-13]. Renal toxicity is the most cited problem and is reported between 9-50% of cases treated with IV Cidofovir and rarely even with intravesical usage [12,14-16].

Lack of awareness of BKPyV-HC post HCT and cost constraints has precluded the use of Cidofovir until the latter half of the last decade in the country. This research aimed to study the use of cidofovir in post-HCT-BKPyV infection, and understand the differences, if any, between innovator cidofovir used between 2015 and 2019 and the Indian Generic molecule used since its availability in the latter part of 2019.

MATERIALS AND METHODS

The present study was a retrospective cohort study, conducted at the Department of Haematology and Virology at the Christian

Medical College, Vellore, a tertiary care centre in South Indian. All patients diagnosed with BKPyV-HC post HCT and treated with cidofovir between October 2015 and May 2021 were included in the study. The analysis of the data was done in June 2021. Patients with BKPyV-HC who were not treated with cidofovir were excluded. The Institutional Review Board approved this retrospective analysis at Christian Medical College, Vellore, India [IRB Min.No. 13226 [Retro] dated 22.07.2020].

Study Procedure

As a department policy, for patients undergoing a Matched Sibling Donor (MSD) transplant, BKPyV PCR was performed on urine if they developed symptoms suggestive of cystitis along with either microscopic or gross haematuria. In patients undergoing haploidentical (Haplo) and Matched Unrelated Donor (MUD) transplants, BKPyV PCR in the urine was monitored every week following engraftment until D+100 post HCT. A value higher than >7 log10 copies/mL with no other aetiology for symptoms and signs was diagnostic of BKPyV-HC [4].

The conditioning regimens, graft source, and Graft versus Host Disease (GVHD) prophylaxis varied depending upon the indication for HCT. Acute GVHD was graded with the Glucksberg criteria [17], and chronic GVHD with the National Institutes of Health (NIH) consensus criteria [18]. Following a diagnosis of acute GVHD, patients were initiated on corticosteroids and calcineurin inhibitors. We treated steroid refractory GVHD with Mycophenolate mofetil, Cyclophosphamide, Basiliximab, Ruxolitinib or Etanercept as per the discretion of the treating physician.

Haemorrhagic cystitis: Grading of the severity of HC was reported as described by Droller MJ et al., in the context of cyclophosphamide-induced HC but is also presently used for all other aetiologies [19]. In summary, grade I include microscopic bleeding (not visible), grade II has visible bleeding, grade III is bleeding with small clots, and grade IV is bleeding with clots large enough to cause obstruction. Grade I and II are termed early HC, while grade III and IV is defined as severe HC [20]. Imaging results, if available, were reviewed for signs compatible with BKPyV infection and categorised into five groups: bladder wall thickening, urinary clots and, or haemorrhage, hydronephrosis, perivesical stranding, and ureteral thickening [21].

CMV load was measured weekly after engraftment until day 100, and ganciclovir was initiated when copy levels were more than log 3 or >1000 copies/mL [22].

All patients received supportive care with intravenous hydration, bladder relaxants, and platelet support to target a platelet count of at least 30-50×10^9/L to prevent gross haematuria for all cases. Intravenous immunoglobulin replacement was administered routinely on Day 7 post HCT in those undergoing haploidentical or MUD transplants. We gave repeat doses if BKPyV-HC developed and the IgG level was less than 700 mg/dL per institutional standard international reference range [23].

Cidofovir: Innovator Cidofovir (375 mg/5 mL; Heritage Pharmaceuticals, USA) was used between 2015 and 2019, and from 2020 onwards, Generic Cidofovir (Cidnavir- 375 mg/5 mL; Emcure Pharmaceuticals, India). The decision to initiate treatment of BKPyV-HC with Cidofovir was left to the individual treating physician's discretion and ranged from asymptomatic BKPyV viruria to gross HC. Cidofovir was administered IV at 5 mg/Kg with probenecid and IV hydration of normal saline pre and postinfusion. Intravesical Cidofovir was given at 1 mg/kg via a triple lumen bladder irrigation catheter, following which the catheter was clamped for one hour and then released. Cidofovir was repeated weekly if the renal functions were normal in the absence of toxicity. Cytopenia post cidofovir was defined as a decrease in Absolute Neutrophil Count (ANC) to less than 1.5×10^9/L occurring anytime within one week of Cidofovir therapy. Acute kidney injury was defined as per Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury [24].

STATISTICAL ANALYSIS

The descriptive data were reported as means with Standard Deviation (SD) (medians and interquartile range for non parametric distributions) or frequencies with percentages as appropriate. Continuous data was compared with the t-test or Mann-Whitney U test as appropriate. Proportions were compared using the Pearson Chi-square test or Fischers-exact test. Analysis of risk factors for survival and co-occurrence of BKPyV-HC was calculated using Cox regression proportional hazards method. The Kaplan-Meier method was used to estimate overall survival, and comparisons were based on the log-rank test. For all tests, a 2-sided p-value of 0.05 or less was considered statistically significant. Data was analysed using the International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) statistics version 24.

RESULTS

A total of 985 patients underwent allogeneic stem cell transplantation at CMC Vellore, India, of which 67 patients (6.8%) were treated with BKPyV-HC with Cidofovir. At the time of this analysis, 47.8% (32) had died, and the common causes of death were acute GVHD with infection (16, 23.9%). The four patients who died of infections had fungal pneumonia, bacterial pneumonia, Vancomycin-resistant enterococcal sepsis (VRE sepsis), and drug resistant Non Fermentative Gram Negative Bacilli (NFGNB) septicaemia. Baseline characteristics and details on HC are described in [Table/Fig-1,2], respectively.

Characteristics	Total number of patients (n=67)	Innovator cidofovir (n=47)	Generic cidofovir (n=20)	p-value
Median age (range)-yrs	22 (2-63)	22 (2-55)	29 (4-63)	0.294
Sex- n (%)				
Male	51 (76.1)	37 (78.7)	14 (70)	0.534
Female	16 (23.9)	10 (21.3)	6 (30)	
Diagnosis- n (%)				
Malignant	50 (74.6)	32 (68)	18 (90)	0.311
Non malignant	17 (25.4)	15 (32)	2 (10)	
Donor source- n (%)				
MSD	7 (10.5)	4 (8.5)	3 (15)	0.005
MUD	30 (44.8)	16 (34.1)	14 (70)	
Haploidentical	27 (40.3)	24 (51.1)	3 (15)	
MRD (non-sibling)	3 (4.4)	3 (6.3)	0	
Conditioning regimens- n (%)				
Myeloablative	44 (65.7)	33 (70.2)	11 (55)	0.014
Non Myeloablative	23 (34.3)	14 (19.8)	9 (45)	
Disease status- n (%)				
Partial remission	5 (11.9)	2 (7.4)	3 (20)	<0.001
Complete remission	35 (83.3)	25 (92.5)	10 (66.7)	
Active disease	2 (4.8)	0	2 (13.3)	
Median CD34 cell dose-n×10^6/kg (range)	10 (4.3-21.60)	9.68 (4.30-16.60)	10.05 (5.80-21.60)	(0.231)
Outcomes n (%)				
Dead	32 (47.8)	23 (48.9)	9 (45)	0.796
Alive	35 (52.2)	24 (51.1)	11 (55)	
Cause of death n (%)				
Acute GVHD with infection	16 (23.9)	14 (60.9)	2 (22.2)	0.248
Relapse	8 (11.9)	5 (21.7)	3 (33.3)	
Infection	4 (6)	2 (8.7)	2 (22.2)	
Graft failure	2 (3)	1 (4.3)	1 (11.1)	
Others	2 (3)	1 (4.3)	1 (11.1)	

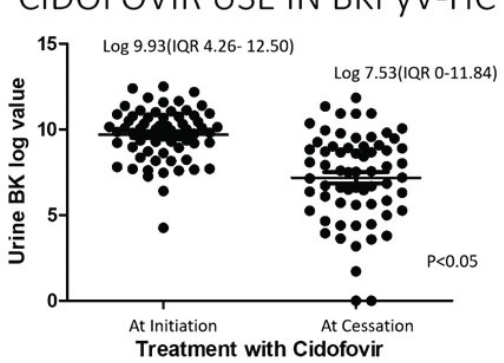
Acute GVHD n (%)				
Yes	54 (80.6)	42 (89.4)	12 (60)	0.029
No	12 (17.9)	5 (10.6)	7 (35)	
Not applicable	1 (1.5)	0	1 (5)	
Chronic GVHD- n (%)				
Yes	28 (41.8)	21 (44.7)	7 (35)	0.743
No	17 (25.4)	12 (25.5)	5 (25)	
Not applicable	22 (32.8)	14 (29.8)	8 (40)	

[Table/Fig-1]: Baseline characteristics.
MSD: Matched sibling donor; MUD: Matched unrelated donor; MRD: Matched related donor; GVHD: Graft versus host disease

Characteristics	Total cidofovir	Original	Indian	p-value
Grade of HC- n (%)				
Grade 1	20 (29.9)	12 (25.5)	8 (40)	0.244
Grade 2	12 (17.9)	11 (23.5)	1 (5)	
Grade 3	22 (32.8)	16 (34)	6 (30)	
Grade 4	13 (19.4)	8 (17)	5 (25)	
Clinical resolution- n (%)				
No	20 (29.9)	11 (23.4)	9 (45)	0.145
Yes	47 (70.1)	36 (76.6)	11 (55)	
Treatment initiation at early HC n (%)				
Yes	32 (47.7)	20 (42.6)	12 (60)	0.437
No	35 (52.3)	27 (57.4)	8 (40)	
Radiological findings- n (%)				
Normal imaging	25 (37.3)	17 (36.2)	8 (40)	0.627
Bladder wall thickening	15 (22.4)	12 (25.5)	3 (15)	
Urinary clots and or haemorrhage	12 (17.9)	7 (14.9)	5 (25)	
Hydronephrosis	11 (16.4)	7 (14.9)	4 (20)	
Ureteral thickening	2 (3)	2 (4.3)	0	
No imaging performed	2 (3)	2 (4.3)	0	

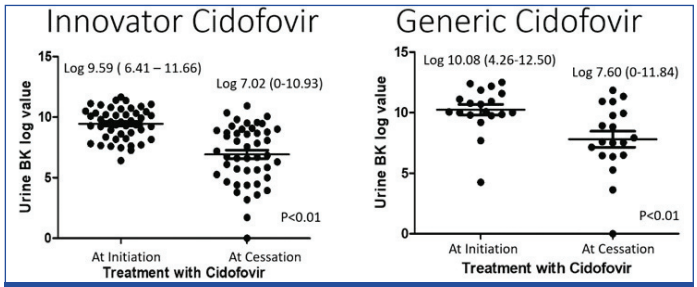
[Table/Fig-2]: Haemorrhagic cystitis in BKPyV.
HC: Haemorrhagic cystitis

Cidofovir treatment: The median number of doses of cidofovir administered were three (range: 1-10), and the median time to initiation of first dose post-HCT was 47 days (range: 6-268). The median BKPyV log value at the time of treatment initiation was 9.93 (4.26-12.50), and the median BKPyV log value at the time of cessation of treatment was 7.53 (0-11.84) [Table/Fig-3a]. A reduction in viruria was observed in 55 (82%) patients, while nine patients (13.4%) did not respond to Cidofovir. The response was not evaluable in three patients as they succumbed very early post-transplant. Post-Cidofovir, cytopenia was seen in 34 (50.7%), acute kidney injury in 4 (8.51%) and a combination of both was seen in 19 (28.3%). Nine patients (13.4%) did not have any complications with the use of cidofovir. One patient was given intravesical cidofovir after the second transplant in the setting of severe cytopenia and AKI on renal replacement therapy.



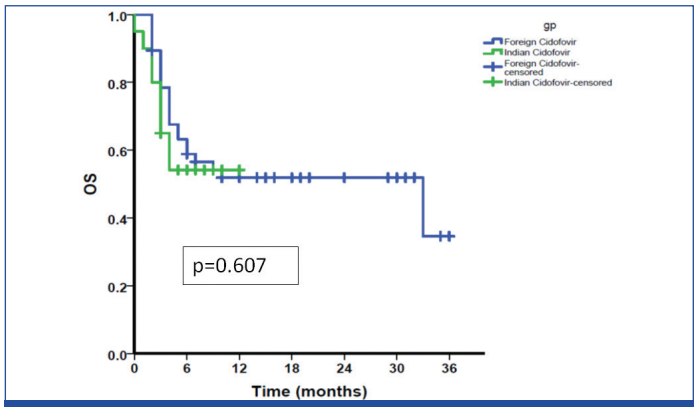
[Table/Fig-3a]: Cidofovir use leads to a significant reduction in BKPyV log levels.

From the time of initiation to the end of cidofovir treatment, there was a significant (p<0.01) decrease in log BKPyV values in both innovator (9.59-7.02) and generic (10.08-7.60) treatment groups [Table/Fig-3b].



[Table/Fig-3b]: Innovator and generic cidofovir use leads to a significant reduction in BKPyV log levels.

Comparison between innovator and generic cidofovir: There were no significant differences in the baseline characteristics (age, gender, donor source or CD34 stem cell dose) or overall survival [Table/Fig-4] of the patients treated with the innovator molecule or Generic drug. Patients undergoing myeloablative conditioning was significantly higher in the innovator group while MUD transplants were significantly higher in the Generic group. There were fewer patients in remission in the Generic group and acute GVHD was seen more commonly in the Innovator group. The median number of doses used (3 in both groups), the time to initiation of therapy and side effects of cidofovir were similar between the innovator and the biosimilar groups. The efficacy in significantly decreasing the log values of BKPyV is seen in both molecules of the drug as depicted in n [Table/Fig-3b].



[Table/Fig-4]: Kaplan-meier survival curves between those treated with innovator and generic cidofovir.
There was no survival difference between the original and innovator cidofovir

Predictors of mortality in BKPyV-HC with cidofovir treatment: Persistent HC (no clinical resolution), CMV reactivation and the presence of any toxicity to cidofovir and a higher median CD34 cell dose was significantly associated with increased mortality. Mortality was significantly lower when patients were initiated on therapy with early HC (grade 1 and 2). [Table/Fig-5] enumerates the significant predictors of mortality on univariate and multivariate logistic regression analysis.

	Univariate		Multivariate	
Characteristics	Risk (95% CI)	p-value	Risk (95% CI)	p-value
CD34 dose >9×10^6/Kg	1.13 (1.013-1.261)	0.029	1.48 (0.983-2.23)	0.061
Partial remission at time of transplant in malignancies	27.9 (4.2-183.2)	0.001	6.55 (0.36-117.5)	0.202
Number of doses of cidofovir (≤3 doses)	0.78 (0.621-0.984)	0.036	0.975 (0.644-1.477)	0.906
BK Value >7 log at stopping therapy	1.20 (1.02-1.42)	0.021	1.31 (0.954-1.810)	0.095
Cytopenia and AKI post cidofovir therapy	4.91 (1.11-21.76)	0.036	0.40 (0.025-6.70)	0.530

Clinical resolution of HC	0.07 (0.028-0.179)	<0.001	0.011 (0.001-0.134)	<0.001
Treatment initiation at early HC	0.46 (0.234-0.936)	0.032	2.23 (0.582-8.588)	0.241

[Table/Fig-5]: Risk factors affecting mortality with BKPyV; univariate and multivariate analysis.
HC: Haemorrhagic cystitis; BK: BK polyoma virus; AKI: Acute kidney injury

DISCUSSION

Treatment of post HCT- BKPyV-HC with cidofovir is an established treatment modality with response rates between 70-100% in various studies [2,8,25]. The doses used, and routes of administration also vary significantly [13]. In our centre, cidofovir use began in late 2015 for those with symptomatic BKPyV-HC, whereby a clinical resolution of 70.1% was observed, which was comparable to published literature [7]. Only 10.5% of present study cohort had a MSD source. Since alternate donor transplants were the majority, previously published factors significantly associated with response to cidofovir, like Peripheral Blood Stem Cell (PBSC) as stem cell source and total body irradiation (as part of conditioning regimen in haploidentical HCT) use was present in a majority of the patients.

Toxicity described with cidofovir include myelotoxicity, nephrotoxicity and ocular complications [2,26]. Creatinine elevation and AKI were seen in 48% of present study and were similar to nephrotoxicity rates (9%-50%) in various studies [8,25]. Since acute GVHD was present in 81.8% of present study, concomitant use of a calcineurin inhibitor may also have contributed to nephrotoxicity [25]. We offset cytopenia with the judicious use of growth factors. However, cytopenia at the onset of symptoms also prolonged BKPyV-HC in a recent study [27]. No definite ocular toxicity was documented, but it is suspected that the presence of chronic GVHD with ocular involvement in two patients may have masked this complication. Intravesical cidofovir was used only in two patients with pre-existing renal dysfunction and renal replacement therapy. Hence, present study cannot comment on the previously described favourable renal-specific toxicity profile [28].

Clinical resolution correlated with survival, and persistent HC (no clinical resolution) was significantly associated with death (94.7% vs 31.9%, p<0.001) [29]. Since BKPyV-HC was not the primary cause of death in any of the cases, this points to the complicated clinical conundrum of GVHD, bacterial and fungal infection, along with multiple organ failures associated with persistent HC and ultimately culminating in death. The balance between decreasing inflammatory damage of GVHD and BKPyV cystitis with immunosuppression and resultant overwhelming drug-resistant and invasive infections is a tightrope [30].

Initiation of cidofovir therapy in the early stages of BKPyV-HC resulted in increased rates of clinical resolution (85.3% vs 56.3%, p=0.014) and has not been studied in the post HCT setting. In kidney transplant recipients, early intervention before the onset of creatinine elevations is recommended to decrease the risk of BKVAN [31]. There was a mortality risk with persistently high BKPyV log levels (>log 7) on univariate analysis. This corroborates the finding that non resolution of HC is strongly associated with death (p<0.001).

In-vivo T-cell depletion with post-transplant cyclophosphamide [32] in haploidentical transplants results in delayed immune reconstitution [33] and may explain the increased susceptibility to viral infections. However, this is not consistently seen as there is a report in the paediatric population whereby CD4 T-cell immune reconstitution did not affect CMV and BKPyV reactivation [34]. In cases where there was simultaneous infection with CMV and BKPyV, we used single-agent cidofovir at 5 mg/kg weekly to treat both the infections.

Persistent malignant disease and failure to reach complete remission emerged as a significant risk factor in univariate analysis. This association of increased post-transplant viral reactivations and disease has been published previously in the literature [35]. Persistent residual disease may be a surrogate marker of immune dysfunction [36].

A higher CD34 cell dose of >9×10^6/Kg emerged as a risk factor for mortality on univariate analysis. This may be a surrogate marker for increased GVHD resulting in greater immunosuppression and the emergence of viral infections. A lower number of cidofovir doses used in those who died with BKPyV-HC may reflect delayed use of the drug, i.e., once grade 3 or 4 HC had set in.

There was no remarkable difference between the innovator and generic cidofovir drug in the outcomes and toxicity. However, there is a major cost difference between the innovator and generic drug (INR 115,500 vs 50,000 per 375 mg/5 mL vial).

Non resolution of HC significantly correlated with mortality, though it was not the primary or secondary cause of death in any case. Some novel factors such as donor's BKPyV genotype [37], urinary shedding rates and recipients BKPyV antibody levels [38] need to be considered to predict those with persistent disease and poor response to cidofovir. Virus-specific Cytotoxic T lymphocytes as an adjunct to cidofovir may prove to be useful in refractory cases [39].

Limitation(s)

The current study shares the limitations inherent to all retrospective analyses in that authors did not follow prespecified uniform protocols to guide treatment. However, complete data capture was possible as it is a single centre experience. To our knowledge, there is no published experience with cidofovir post HCT within our resource-limited setting or with the use of generic Cidofovir.

CONCLUSION(S)

Cidofovir effectively treats BKPyV-HC, and initiation of therapy in early grades of HC was associated with better outcomes, while non resolution had a higher risk of mortality. There are no significant differences in the outcomes and toxicity between the original and generic types, with the latter molecule being much more cost-efficient.

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