Successful Treatment of BK Virus Hemorrhagic Cystitis (HC) Post Allogenic Hematopoietic Stem Cell Transplantation with Low Dose Cidofovir

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Abstract

BK virus (BKV) hemorrhagic cystitis (HC) is a serious cause of morbidity and mortality after allogeneic hematopoietic SCT (allo-HSCT) in patients with hematological malignancies. Around half of allogenic HSCT patients present with BKV viruria at some point after HSCT; about 5–40% of these patients subsequently develop active HC. Supportive care including bladder irrigation, blood transfusions and symptomatic pain management remains the mainstay of therapy; the acyclic nucleoside analogue cidofovir is currently the front-line drug for BKV-HC treatment. Here we report the first case of severe hemorrhagic cystitis from India who was successfully treated with low dose cidofovir therapy.

Introduction

BK virus (BKV) is a human Polyomavirus. Primary infection usually occurs during childhood. BKV remains in a latent state, mostly in the kidneys, urinary tract and peripheral blood leukocytes.1 Seroepidemiological studies have shown a very high (>90%) seroprevalence among adults worldwide. BKV reactivation is likely to occur during the immunodeficiency states such as during the immunosuppressive therapy after allogeneic HSCT. BKV nephropathy has emerged as a significant and often severe complication in kidney transplantation.1,2 Around half of allogenic HSCT patients present BKV viruria at some point after HSCT. About 5–40% of the patients subsequently develop active HC.1,2 In the HSCT setting, the risk factors associated with BKV-HC development are allogeneic versus autologous HSCT, myeloablative conditioning, unrelated donor transplants, cord blood transplantation and pre-transplantation BKV serology measured by a quantitative method.2,3 Standard treatment for BKV-HC has not been established yet. Supportive approaches include bladder irrigation, blood transfusions and symptomatic pain relief treatment; the acyclic nucleoside analog cidofovir is currently the front-line drug for BKV-HC treatment.1–5 Alternative strategies are hyperbaric oxygen therapy, leflunomide6 and fluoroquinolone7 antibiotics. In very severe cases, urological intervention such as cautery, embolization or cystectomy may be necessary.

Case Report

A 42 years old male, with Acute Myeloid Leukemia, t(6;9), underwent myeloablative (Bu-Cy conditioning with cyclosporine/methotrexate as GVHD prophylaxis), matched sibling donor peripheral blood allogeneic stem cell transplant in first complete Remission (CR1). His early post transplant course was complicated by isolated grade 2 acute gut GVHD which responded to corticosteroid therapy. On day 30 post transplant, he developed dysuria, urinary frequency, and urgency which progressively worsened and patient was then admitted on day 35 due to severe dysuria resulting in urinary retention. At the same time, he developed maculopapular rash over the face, back and chest s/o of skin GVHD. He also had oral Candidiasis.

He was treated with intravenous hyperhydration, patient controlled analgesia (PCA), urinary catheterization and antifungal. Corticosteroid dose was increased in keeping with the development of acute skin GVHD. Urine examination showed microscopic hematuria, no pus cells; and urine culture was sterile. Hemorrhagic cystitis was suspected and urine CMV, BK Polyoma virus and adenovirus PCR was done which showed urine BK virus to be strongly positive (60.75 million copies/ml) while blood CMV, and BK Viruses were not detectable. Skin GVHD and oral candidiasis rapidly improved but urinary symptoms persisted so rapid tapering of steroid was started to help the rapid immune reconstitution with the hope of controlling the BK virus proliferation. Cidofovir is an antiviral drug, which has shown efficacy against many viruses including BK virus. Unfortunately cidofovir is not available in India and it has to be imported from outside. Leflunamide, an immunomodulatory drug has shown activity against BK virus in few case reports. Leflunamide (100mg loading followed by 20mg once a day) was given for 7 days in the hope of decreasing BK virus load however the repeat BK virus load increased to 3060 million copies/ml. More importantly patient’s urinary symptoms worsened with the development of frequent, severely painful urinary bladder cramps, macroscopic hematuria and passage of small blood clots. A urology consultation was done, cystoscopy (Figure 1) was performed, and biopsy was taken which revealed severe hemorrhagic cystitis. Foley’s catheter was then removed and continuous bladder irrigation (CBI) was done through another catheter with normal saline but symptoms did not improve. At the same time we were able to arrange Cidofovir for this patient.

On day 45, treatment with low dose Cidofovir protocol was started (2 mg/kg 1st dose followed by 1 mg/kg weekly...
without probenecid). Intravesical administration of cidofovir through CBI catheter was also done on the same day by adding cidofovir 1 mg/kg in 50 ml of normal saline and clamping the outlet for 1 hour. There was rapid improvement in symptoms of bladder spasms after the 1 week of Cidofovir therapy coinciding with substantial reduction in urine B K virus load to 52 million copies/ml. On day 52, second dose of intravenous cidofovir was given. By the day 58, we were able to remove bladder irrigation catheter. Thereafter urinary frequency and dysuria progressively improved and patient was discharged just after the 3rd dose of Cidofovir and planned 4th dose of Cidofovir was given on the follow up visit in day care. Cidofovir therapy was well tolerated without any evidence of renal toxicity. After 4th week of therapy patient had no symptoms with BKV being undetectable (Figure 2). At present patient is 10 months of post-transplant, in clinical remission, on ongoing immunosuppression with Tacrolimus, Mycophenolate and prednisolone for oral chronic graft versus host disease but without any clinical recurrence of hemorrhagic cystitis.

Discussion

BK virus is a polyoma virus and primary infection occurs during childhood, and 75–80% of adults have antibodies. BKV then establishes latency primarily in the genitourinary tract, and viral reactivation generally occurs in immunocompromised patients. BKV is an important pathogen and cause of nephropathy in recipients of renal transplant. BKV reactivation after allogeneic HSCT is associated with manifestations ranging from asymptomatic viruria to severe hemorrhagic BK virus load after starting cidofovir therapy

**Conclusion**

BKV-HC is an emerging viral complication post-allo-HSCT and is associated with significant morbidity. Monitoring of BK viremia in high-risk patients should improve early detection of this complication. Early identification and prompt antiviral management may improve the outcome.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

**References**


**Fig. 1: Cystoscopy: Features s/o of severe acute cystitis**

**Fig. 2: Serial urine BK virus load after starting cidofovir therapy**