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Mini review

BK Virus Infection in Solid-Organ and Hematopoietic Stem Cell Transplant Recipients

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Abstract

BK virus is one of several polyomaviruses capable of causing clinically significant infection in humans. Infection is asymptomatic, but reactivation in immunocompromised patients can cause significant clinical illness: hemorrhagic cystitis in hematopoietic stem cell transplant recipients and nephropathy in renal transplant recipients. The primary management of BK virus disease in immunocompromised patients is reduction of immunosuppression. We review the current landscape of active treatment of BK virus disease in immunocompromised patients.

Keywords: BK virus; BK nephropathy; Hemorrhagic cystitis; Solid organ transplantation; Hematopoietic stem cell transplantation

Abbreviations: BKV: BK virus; HCT: Hematopoietic stem cell transplant; rH-KGF: recombinant human keratinocyte growth factor; VST: virus-specific T-cell therapy

Introduction

BK virus (BKV) is one of several polyomaviruses capable of causing clinically significant infection in humans. Other human polyomaviruses include JC virus, Kl polyoma virus, WU polyoma virus, Merkel cell polyoma virus, and trichodysplasia spinulosa virus [1]. Polyomaviruses are small, nonenveloped dsDNA viruses that are widespread in nature and cause infections worldwide [2,3]. These viruses become latent and can reactivate during periods of immunosuppression [2,3].

BKV was first isolated in 1971, from a urine sample of a renal transplant patient with ureteral stenosis [1]. The virus is most likely transmited through mucosal contact and establishes latency in the kidney and uroepithelial cells [4]. Infection is common, with up to 98% seropositivity worldwide [3,4]. Initial infection typically occurs in childhood and is asymptomatic [2,4]. However, reactivation in immunocompromised patients can cause significant clinical illness, most commonly hemorrhagic cystitis in hematopoietic stem cell transplant (HCT) recipients and nephropathy in renal transplant recipients [1].

BKV hemorrhagic cystitis typically presents in HCT patients 2-8 weeks post-transplant with dysuria, lower abdominal pain, urinary frequency, and hematuria. Earlier presentations of hemorrhagic cystitis (< 1 week) are more likely to be secondary to adverse effects of conditioning regimens, such as cyclophosphamide [7]. Hemorrhagic cystitis can lead to complications including clot formation in the bladder, obstructive hydronephrosis, and life-threatening bleeding in HCT recipients. BKV nephropathy will

present with worsening renal function and potentially loss of the renal allograti in transplant recipients [5,6].

Diagnosis of BKV hemorrhagic cystitis requires compatible clinical symptoms, macroscopic hematuria with or without urinary clots, and BK viruria of >7 log10 copies/mL (>10 million copies/mL) [5]. Presumptive diagnosis of BK nephropathy may be made with compatible clinical presentation and persistent BK DNAemia of >4 log10 copies/mL (>10,000 copies/mL) [6]. Definitive diagnosis of BK nephropathy requires a renal biopsy demonstrating positive staining polyomavirus proteins, cytopathic changes in renal tubules, and interstitial nephritis [5].

Unfortunately, treatment options for BKV are limited. The mainstay for managing BKV is reduction of immunosuppression and supportive care including pain management, hydration, and transfusions [7]. Intravenous cidofovir, leflunomide, fluoroquinolones, and IVIG have been suggested as management options, though proper randomized clinical trials are lacking, meta-analysis demonstrated no benefit, and these medications carry risk of adverse effects, limiting routine use [6]. Recently, several newer therapies have emerged as potential management options. These therapies include viral-specific T-cells, keratinocyte growth factor, and hyperbaric oxygen therapy.

Virus-specific T-cells (VSTs) are developed from either the patient's donor or third-party donors. Peripheral blood mononuclear cells from the donor are then stimulated to produce virus-reactive T-cells, which are then infused into the patient [8]. Studies evaluating VSTs in treatment of hemorrhagic cystitis in HCT patients have shown promising results [9-12]. One small study evaluated third-party BKV-specific T-cells for management of BKV hemorrhagic cystitis following allotransplantation and found that 70% of patients developed partial or complete response to therapy within 45 days of infusion. Median time to response was 2-3 weeks, and no patients developed de novo grade 3 or 4 GVHD, grati failure, or infusion-related toxicities [10]. Fewer studies have evaluated VSTs in treatment of BKV nephropathy in renal transplant recipients. One study administered VSTs to two pediatric renal transplant recipients, one of whom was also a heart transplant recipient. The renal transplant recipient responded with reduction in BK DNAemia and no grati rejection. The heart-renal transplant recipient cleared BK DNAemia and was able to receive a second renal transplant [9].

Recombinant human keratinocyte growth factor (rH-KGF), while not an antiviral therapy, has shown some promise in management of hemorrhagic cystitis. Several case reports have been published. In one report, a 16-year-old patient with BKV hemorrhagic cystitis following matched-sibling HCT for myelodysplastic syndrome appeared to respond to rH-KGF within 48 hours, atier failing therapy with ciprofloxacin, estrogen, intravesicular cidofovir, and multiple cystoscopies [13]. Another case report described a 12-year-old patient with BKV hemorrhagic cystitis following matched-unrelated donor HCT for acute myeloid leukemia. This patient failed to respond to cystoscopy, intravenous and intravesicular cidofovir, prostaglandin E2, continuous bladder irrigation, and hyperbaric oxygen therapy. One week following initiation of rH-KGF therapy, the patient noted symptomatic improvement [14].

Hyperbaric oxygen therapy (HBOT) has been used for many indications, including carbon monoxide poisoning, crush injury, diabetic foot lesions, and refractory chronic osteomyelitis [15]. One small study evaluated patients with hemorrhagic cystitis secondary to either BKV or adenovirus hemorrhagic cystitis (6 with BKV and 2 with adenovirus in both treatment and control groups). Patients receiving HBOT had a faster median time to complete resolution (14.5 days vs 24 days) and a higher response rate (100% vs 62.5%) when compared to the control group. No severe HBOT-related adverse effects were noted [16]. Case reports have reported similar promising results [17,18].

Except for VST for the treatment of BK hemorrhagic cystitis, which is not universally available, evidence-based and effective active treatments for BKV hemorrhagic cystitis or nephropathy are lacking. Treatment of BKV in immunocompromised patients is ripe for investigation and multicenter collaboration.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

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