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Antibodies to BK virus in children prior to allogeneic hematopoietic cell transplant

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Abstract

BK virus (BKV) is associated with kidney and bladder disease after hematopoietic cell transplantation (HCT) but less is known about the seroprevalence of pre-transplant antibodies to BKV in children. We measured BKV IgG antibody titers in 36 children before HCT. BKV IgG antibodies were detected in all 36 patients, with 28/36 (77.8%) developing BK viremia in the first 100 days. Pre-HCT BKV IgG antibody titers >1:40,960 were protective against later BK viremia 10,000 copies/mL. The seroprevalence of antibodies to BKV is high in children undergoing HCT and post-transplant BK viremia, which is associated with bladder and kidney injury, is common.

Keywords

BK virus; hematopoietic cell transplant; humoral immunity; pediatrics

INTRODUCTION

The polyomavirus BK (BKV) infects kidney and bladder cells and can reactivate in immunosuppressed patients [1]. BKV is associated with nephropathy in kidney transplant recipients and with hemorrhagic cystitis and nephropathy after hematopoietic cell transplantation (HCT) [2, 3].

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Conflict of Interest Statement

Dr. Hester is an employee of Viracor-IBT Laboratories, which performed the BKV antibody testing free of charge.

In healthy children, the seroprevalence of BKV infection approaches 90% by 10 years of age [4, 5]. While studies have examined BKV antibodies in children prior to kidney transplant [6–8], in HCT recipients, less is known about whether BKV antibodies confer protection against later disease [9–11].

We describe BKV antibodies in children prior to allogeneic HCT and the association between pre-HCT titers and post-HCT BK viremia. We focused on the development of BK viremia $\geq 10,000$ copies/mL because this degree of viremia is more specific than viruria for bladder and kidney injury after transplant [2, 3].

METHODS

Study population

We analyzed 100 consecutive children and adolescents receiving a HCT at Cincinnati Children's Hospital Medical Center (CCHMC) from September 2010 to December 2011 who were followed until 100 days after transplant [12] and were originally enrolled to study thrombotic microangiopathy [13]. We included 36 patients after excluding 10 patients undergoing autologous HCT, 2 not consenting to have their samples used for any purpose, 2 without baseline serum available, and 50 who had received pre-HCT intravenous immune globulin (IVIG), which contains antibodies to BKV [14]. The CCHMC Institutional Review Board approved the study.

BKV antibody testing

Serum obtained a median of 6 days (interquartile range (IQR) 5–8.5 days) prior to stem cell infusion was frozen (-80°C) and later tested for BKV IgG antibodies. Antibodies to BKV were measured at Viracor-IBT Laboratories (Lee's Summit, Missouri) [6]. The assay reports titers ranging from 1:640 to $>1:163,840$ against the VP1 capsid.

BKV PCR testing

Polymerase chain reaction (PCR) testing for BK viremia was performed clinically for unexplained hematuria, cystitis, and/or an elevation in serum creatinine. This was supplemented with an analysis of stored plasma samples from those without clinical testing results [12]. Plasma was stored (-80°C) weekly while inpatient and at day 100. These stored samples were tested so that each patient *with available plasma* had at least three BKV PCR results: at least one measured between days 0–14, 15–85, and 100 ± 14 days post-HCT. The 36 patients had a median of 12 (IQR 3.5–20 tests) plasma BKV PCR tests. All BKV PCR testing was performed at CCHMC using genomic sequence targets common to all BKV genotypes.

Outcome definition

The exact BK viremia PCR cutoff associated with clinical disease is not known [15]. Nevertheless, a blood PCR $\geq 10,000$ copies/mL is sensitive and specific for biopsy proven BKV nephropathy after kidney transplant [2]. We previously reported that higher grade BK viremia ($\geq 10,000$ copies/mL) was also associated with kidney injury and hemorrhagic cystitis after HCT [3, 12]. We therefore categorized post-HCT BK viremia using each

subject's peak plasma PCR as 0–9,999, 10,000–100,000, or >100,000 copies/mL [12]. BK viremia has a higher positive predictive value for clinically relevant disease than viruria [2, 3, 7, 12, 16], but we also reported information on viruria, when available.

Analyses

We compared categorical variables with the Fischer exact test and continuous variables with the Wilcoxon rank-sum test. Data were collected using Research Electronic Data Capture [17] and analyzed with STATA (version 12, College Station, Texas).

RESULTS

The clinical characteristics of the 36 patients undergoing HCT are shown in Table I, of whom 5 (13.9%) had a pre-HCT BKV IgG titer=1:2,560, 17 (47.2%) had a titer=1:10,240, 7 (19.4%) had a titer=1:40,960, 6 (16.7%) had a titer=1:163,840, and 1 (2.8%) had a titer>1:163,840.

BK viremia >0 copies/mL was detected in 28 (77.8%) recipients. Among the 36 patients, the peak BKV blood PCR was 0–9,999 copies/mL in 26 (72.2%), was 10,000–100,000 copies/mL in 5 (13.9%), and was >100,000 copies/mL in 5 (13.9%) patients (Supplemental Table I).

The association between pre-transplant BKV antibody titers and post-transplant BK viremia is shown in Figure 1, illustrating that none of the 7 HCT recipients with a pre-transplant titer >1:40,960 developed BK viremia >10,000 copies/mL ($p=0.16$).

There were 8 cases (22.2%) of cystitis, with 7/8 (87.5%) in patients with a titer = 1:40,960 ($p=1.0$). Of these 8 cases, 4 (50.0%) had a peak BK blood PCR of <10,000 copies/mL and 4 (50.0%) had a peak BK blood PCR of ≥10,000 copies/mL. In the 29/36 (80.6%) patients with day 100 data, the median (IQR) creatinine-estimated glomerular filtration rate was 93.8 (87.6–97.6 mL/min/1.73m²) in the 9 patients with a peak BK blood PCR of <10,000 copies/mL and was 109.4 (87.9–140.7 mL/min/1.73m²) in the 20 patients with a peak BK blood PCR of ≥10,000 copies/mL ($p=0.11$).

DISCUSSION

All 36 children undergoing HCT had BKV antibodies, post-transplant BK viremia was common, and higher baseline titers were associated with protection against BK viremia >10,000 copies/mL.

Koskenvuo et al [9] reported BKV antibodies in 6 children developing cystitis after HCT and found that increasing titers were associated with less severe disease. Titers increased in 4 children with decreasing BK viremia and resolution of cystitis. In the remaining 2 children, BKV titers did not increase, viremia persisted, and cystitis continued.

The literature regarding BK viruria is conflicting. Drummond et al [11] found that pre-HCT BKV titers were high in those with viruria but decreased in those without viruria. Bogdanovic et al [10] observed that 87% of 45 children undergoing HCT were seropositive

for BKV IgG pre-transplant, but antibody titers did not predict later cystitis. Wong et al [18] reported a higher pre-transplant BKV titer was associated with an *increased* risk of viruria in 76 adult HCT recipients, but there was no association between the titer and cystitis. Finally, Lee et al measured BKV antibodies in 98 adults undergoing HCT and reported that increasing titers were associated with viruria. Using the same assay as our analysis and similar to our findings, all 98 subjects (100%) had a detectable BKV IgG of >1:640 [19].

Antibodies against BKV may neutralize infection or signal cell-mediated viral control [9, 20]. After cell attachment, endocytosis of BKV occurs relatively slowly, potentially allowing time for neutralizing antibodies to prevent viral entry [21]. Alternatively, antibodies may clear BK viremia but be less effective at the site of tissue injury [22].

Reduction of immunosuppression is the most effective treatment for BKV [1, 23, 24], but may not be feasible in HCT recipients at risk for graft versus host disease. Novel strategies may include using IVIG, a BKV vaccine, or infusion of virus-specific T-cells [14, 25–27].

BKV infection after HCT is associated with significant kidney and bladder disease [3, 12]. While our observations are limited by a small sample and a *post hoc* analysis of a completed cohort, we observed that higher pre-transplant BKV titers were associated with a lower risk of high grade BK viremia. In contrast to other viruses (CMV), guidelines do not support routine monitoring for BKV antibodies or screening for infection after HCT because currently available treatments are often ineffective [28]. However, as novel therapies become available, such as the infusion of T-cells [27] or a vaccine [26], it will be important to target patients at highest risk for disease. Studies are needed to test if BKV-related disease could be predicted by measuring pre-transplant antibodies and following blood PCR levels after HCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BKV	BK virus
HCT	Hematopoietic cell transplant
PCR	Polymerase chain reaction

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Figure 1.

Association between pre-transplant BKV IgG antibody titers and post-HCT BK viremia in 36 children and young adults undergoing HCT

Table I

Characteristics of the 36 children undergoing allogeneic hematopoietic cell transplant

Age (years)	7.9 [5.1–14.6]
Male gender	20 (55.6%)
Diagnosis group*	
Bone marrow failure	16 (44.4%)
Malignancy	14 (38.9%)
Metabolic	3 (8.3%)
Immunodeficiency	2 (5.6%)
Sickle cell anemia	1 (2.8%)
Donor Cell source	
Un-Related	25 (69.4%)
Related	11 (30.6%)
Donor Cell product	
Marrow	22 (61.1%)
Peripheral blood	8 (22.2%)
Cord blood	6 (16.7%)
Conditioning therapy	
Myeloablative (versus reduced intensity)	27 (75.0%)
Conditioning agents received (yes versus no)	
Total body irradiation	6 (16.7%)
Cyclophosphamide	27 (75.0%)
Alemtuzumab	6 (16.7%)

Data shown as median [interquartile range] or n (%).

* Underlying diagnoses (number of patients): Bone marrow failure: Fanconi anemia (7), myelodysplastic syndrome (3), aplastic anemia (3), dyskeratosis congenita (2), congenital macrothrombocytopenia (1); Malignancy: acute myelogenous leukemia (6), acute lymphoblastic leukemia (4), biphenotypic leukemia (1), non-Hodgkin lymphoma (1), juvenile myelomonocytic leukemia (1), myelodysplastic syndrome (1); Metabolic: Hurler syndrome (1), metachromatic leukodystrophy (1), Krabbe disease (1); Immunodeficiency: chronic granulomatous disease (1), Wiskott-Aldrich syndrome (1)