Transient versus Persistent BK Viremia and Long-Term Outcomes after Kidney and Kidney–Pancreas Transplantation

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Abstract

Background and objectives The objective was to study the long-term impact of transient versus persistent BK viremia on kidney transplant outcomes.

Design, setting, participants, & measurements In total, 609 recipients who underwent kidney transplant from 2007 to 2011 were screened at months 1–12 for the occurrence of polyomavirus BK viremia; 130 patients (21.7%) developed BK viremia during the first year post-transplant. BK viremia patients were classified according to duration of infection (more or less than 3 months), and BK viral loads (more or less than 10,000 copies/ml) were classified as transient low viremia (n=42), transient high viremia (n=18), persistent low viremia (n=23), and persistent high viremia (n=47). All patients were followed a median of 36 (3–66) months. The rates of BK polyomavirus–associated nephropathy, acute rejection, and 1-year graft function were compared with the polyomavirus BK–negative control group.

Results Patient and graft survival were not significantly different among the groups. Graft function (creatinine; milligrams per deciliter) at 1 year was significantly worse in the persistent high viremia (1.75±0.6) and transient high viremia (1.85±0.7) groups compared with aviremic controls (1.47±0.4; P=0.01 and P=0.01, respectively). The incidence of BK polyomavirus–associated nephropathy was limited to the persistent high viremia group (1.3%, P<0.001). The transient high viremia (50%) and persistent high viremia (34%) groups showed significantly increased incidence of acute rejection versus aviremic controls (21.5%), transient low viremia (19%), or persistent low viremia (17.3%) groups.

Conclusion Low viral load BK viremia, either transient or persistent, was not associated with long-term transplant outcomes. Persistent high viremia was associated with a greater risk for BK polyomavirus–associated nephropathy and subsequent graft dysfunction. Although transient high viremia was not associated with BK polyomavirus–associated nephropathy, it was associated with worse graft function. These data support the role of surveillance for BK viremia after transplant.

Introduction

Reactivation of the human polyomavirus BK (BKV) after kidney transplantation can be a serious source of morbidity, with incidence rates reported to range from 20% to 40% (1–3). BKV-associated nephropathy (BKVAN) after reactivation is reported in up to 10% of patients with BKV infection, and it represents a significant cause of graft dysfunction and even premature graft loss in over one half of the cases (4). It has been reported that the course of the disease evolves from reactivation of the BKV in the urinary tract to low copy number viremia to persistent high viremia to tubular interstitial nephropathy (BKVAN) to graft dysfunction and, ultimately, to graft loss (1,5,6). Moreover, the intensity and the duration of BKV infection have been linked to the subsequent effect of the virus on kidney graft outcomes. A few reports have suggested that persistent BK viremia >10,000 copies/ml may be predictive of BKVAN and its subsequent negative impact on the transplanted kidney (1,7,8). To date, there is limited data confirming whether transient BK viremia, especially with high BKV viral loads, has a similar negative effect on long-term patient and graft outcomes. The aim of this study was to investigate the impact of transient versus persistent BK viremia and the intensity of BKV viral loads on both patient and graft survival and long-term graft function.

Materials and Methods

Study Design
This study was designed as a post hoc analysis of prospectively acquired data from 622 patients who...
received a kidney or kidney–pancreas transplant from January 1, 2007, to June 30, 2011, at the Cleveland Clinic Glickman Urological and Kidney Institute. The study was approved by the Cleveland Clinic Institutional Review Board, and it adheres to the Declarations of Helsinki and Istanbul. Thirteen patients were excluded because of early graft loss (<3 months post-transplant) or lack of compliance to the BKV screening protocol. There were 609 kidney (538) and kidney–pancreas (71) recipients that completed follow-up with a functioning graft for at least 3 months, which defined the study population. The study cohort was followed for a median duration of 36 (range=3–66) months.

Immunosuppression
All but two recipients were given induction therapy using either basiliximab (68.4%, n=417) or thymoglobulin (31.1%, n=190). The other two recipients were given alemtuzumab or OKT3. For initial maintenance therapy, calcineurin inhibitors (tacrolimus or cyclosporine) were used in 87.5% (n=534), and mammalian target of rapamycin (sirolimus) was used in 2.4% (n=15) in addition to mycophenolate mofetil (MMF) and prednisone. Tacrolimus and MMF—with prednisone avoidance—were used in 10% (n=60) of recipients. Target immunosuppression trough blood levels in the first 6 months were tacrolimus (6–12 ng/ml), sirolimus (8–12 ng/ml), cyclosporine (175–225 ng/ml), and MMF (2–4 mg/ml). Prednisone was tapered by 3 months post-transplant to 5–7.5 mg/d (Table 1).

Quantitative PCR for BKV-DNA and Surveillance Protocol
Plasma samples for BKV PCR testing were collected monthly during the first 6 months after transplantation and then, at months 8, 10, and 12. Additional tests were done as clinically indicated, with an average of 12.1 tests per patient. Plasma BK viral loads were measured by Mayo Medical Laboratories (Rochester, MN; http://www.mayomedicallaboratories.com/testcatalog/Clinical+and+Interpretive/83187). Primers were directed to the large T antigen gene; the range of detection is 500–10,000 copies/ml.

BK viremia was defined as detecting at least one positive BKV PCR test in the blood. BKV clearance was defined as having no BK viremia for 3 consecutive months. No patient showed recurrence of BK viremia after clearance for 3 consecutive months. The intensity of BK infection was defined according to the duration of viremia (from the onset until clearance) and the peak BK viral load (VL) as follows: transient low viremia, presence of BKV in the blood for less than 3 months with peak VL<10,000 copies/ml; transient high viremia, presence of BKV in blood for less than 3 months with peak VL≥10,000 copies/ml; persistent low viremia, presence of BKV in blood for more than 3 months with peak VL<10,000 copies/ml; and persistent high viremia, presence of BKV in blood for more than 3 months with peak VL≥10,000 copies/ml (1,8–10).

Management of BK Viremia
Active BK viremia mandated review of the patient’s immunosuppressive regimen according to the clinical circumstances. In general, patients who had low levels of BK viremia (VL<10,000 copies/ml) early after transplantation were closely observed and monitored by frequent BKV PCR tests without intervention. If BK viremia did not resolve spontaneously, increasing VLs emerged with subsequent testing, or graft function deteriorated, the dose of immunosuppressive drugs was decreased (30%–50%) or stopped according to the clinical circumstances and the physician’s discretion. Target tacrolimus Cₚ values were 5–6 ng/ml, and MMF doses were 250–500 mg two times per day. Ciprofloxacin (500 mg two times per day) and/or leflunomide were also added in patients with persistent high levels of BK viremia that did not respond to a reduction in immunosuppressive drug doses alone. When used, leflunomide was initiated at 100 mg/d for 5 days followed by a maintenance daily dose of 40 mg/d targeting teriflunomide levels at 40,000–60,000 ng/ml.

Allograft Biopsy
We routinely performed an implant kidney biopsy at the time of transplant. In addition, protocol transplant renal biopsies were done at 3 and 12 months, and cause biopsies were done for unexplained increases in serum creatinine or proteinuria. Of 609 patients, 91.1% (n=555) of patients had a transplant renal biopsy. The remaining 54 patients (8.9%) were unable to complete protocol biopsy or received chronic anticoagulation. Of these patients, 45 patients belonged to the BKV-negative group, 3 patients had persistent low viremia, and 2 patients had transient high viremia.

In situ hybridization testing for BKV was done when recipients had BK viremia or histologic suspicion of viral infection. The diagnosis of BKVAN was made when the biopsy showed the presence of the BK viral genome in the kidney. The diagnosis of acute rejection was made using the BANFF (2005) scoring system. Because of the histologic mimicry between acute rejection and BKVAN, in situ hybridization was also done for all BKV-positive patients who showed acute rejection.

Clinical End Points
The clinical end points compared were the incidence of BKVAN, acute graft rejection, graft loss, and patient death at 12 months according to the presence of transient or persistent BK viremia and BK VLs. Kidney graft function was also analyzed using serum creatinine (SCr; milligrams per deciliter) and eGFR (milliliters per minutes) at 12 months after transplantation using the abbreviated Modification of Diet in Renal Disease equation (11).

Statistical Analyses
Data were collected from the electronic medical records at our transplant center, and, once captured, they were imported into the Research Electronic Data Capture software for easy export and manipulation (12). Kaplan–Meier analyses were applied to determine incidence of acute graft rejection and patient survival. Proportional hazards survival regression analysis (univariate Cox model) was used to compare the incidence of graft rejection and patient and graft survival between groups. All continuous variables were summarized as means and SDs or medians and ranges; the differences were analyzed using the two-sample t or ANOVA test. Categorical variables were
described using frequencies and percentiles, and they were compared using Fisher’s exact/Pearson’s chi-squared test. All tests were performed at a significance level of 0.05, and JMP Pro 10.0.0 software (2012; SAS Institute, Inc.) was used.

### Results

Of the study population, 100% of patients had at least three BKV PCR test results during the first year after transplant, and 88.1% (n=537) of patients completed the 1-year BKV screening protocol as scheduled; 7453 plasma
samples were collected from 609 patients at the scheduled time points for BKV PCR tests. The incidence of post-transplant BK viremia in our population at 1 year was 21% \( (n=130) \), with 81% \( (n=105) \) occurring during the first 6 months after transplant. The incidence of histologically confirmed BKVAN was 1.1% \( (n=7) \). The clearance rate of BK viremia was 77.6% \( (n=101) \), of which 41% \( (n=41) \) occurred spontaneously and 60% \( (n=60) \) occurred after treatment.

**Classification of Patients with Positive BK Viremia**

Among 130 BK viremia patients detected in the first year, 32.3% of patients had transient low viremia \( (n=42) \), 13.8% of patients had transient high viremia \( (n=18) \), 17.7% of
patients had persistent low viremia \((n=23)\), and 36.2\% of patients had persistent high viremia \((n=47)\) as previously defined. Demographic and clinical details for the different groups are provided in Table 1. Seven patients \((1.1\%)\) with histologically confirmed BKVAN were all in the persistent high viremia group \((P<0.001)\).

**BK Viremia and Treatment**

The mean onset of BK viremia was \(4.03\pm2.5\) months post-transplant, with a median BK VL of 3000 copies/ml at onset \((range=500–4,985,000)\) and a peak VL of 9920 copies/ml \((range=500–4,985,000)\). The treatment of BK viremia was as follows: 33\% \((n=43)\) of patients were observed with close monitoring of BKV loads, 37\% \((n=48)\) of patients had immunosuppressive drug dose reduction, 9\% \((n=12)\) of patients had ciprofloxacin added to decrease immunosuppression, 12\% \((n=16)\) of patients had MMF switched to leflunomide, and 9\% \((n=11)\) of patients had both ciprofloxacin and leflunomide added to decreased immunosuppression (Table 2). By definition, the clearance rate was 100\% for both the transient low viremia and transient high viremia groups at 3 months after the onset of BK viremia. The eventual clearance rate (beyond 3 months) for the persistent low viremia group was 78.2\% compared with 48.9\% for the persistent high viremia group. Proportional hazard survival regression analysis showed that persistent low viremia is 3.1-fold more likely to clear the virus compared with persistent high viremia \((HR=3.1; 95\% \text{ CI}, 1.5 \text{ to } 6.5; \ P=0.001)\).

The trough blood levels of the immunosuppressive drugs were carefully monitored, with a total of 26,829...
tests done for mycophenolic acid and 47,066 tests done for tacrolimus. Mean tacrolimus and MMF blood levels were measured pre- and post-BKV for the positive BK viremia groups and before and after 12 months for the aviremic negative control group. Blood levels of immunosuppressive drugs were lowered after BK viremia, with a mean of 23.1% MMF reduction rate (range=16.8%–37.9%) and 16.7% tacrolimus reduction rate (range=9.6%–21.4%). Mean blood levels of MMF and tacrolimus before BK viremia in the positive groups were not significantly higher than the 1-year levels of the same drugs in the negative control group. However, immunosuppressive blood levels after dose reduction were significantly lower in the persistent high viremia group compared with the BKV-negative control group (Table 3).

Clinical Outcomes

The overall patient and graft survival were 95.2% and 92.6%, respectively, at a median follow-up of 36 (range=3–66) months, and they were not significantly different for the five groups stratified by BK viremia persistence and VLs (Figure 1). Biopsy confirmed that acute rejection was diagnosed in 140 patients (22.9%) at any time after transplant, including 85 patients (13.9%) with BANFF borderline findings. Only 72 patients (11.6%) received treatment for acute rejection. The transient high viremia and persistent high viremia groups were associated with the highest graft rejection rates (50% and 34% compared with 21.5% in the BK-negative control group; \(P=0.01\)) (Figure 2). Using a proportional survival regression model, the transient high viremia group had a 2.9-fold greater risk to develop acute rejection compared with the BK-negative group (HR, 2.9; 95% CI, 0.9 to 2.6; \(P=0.09\)). The wide CIs may limit firm conclusions. Comparing graft rejection rates per 100 patients/yr, the transient high viremia group (21.1) and persistent high viremia group (17.9) showed a significantly higher risk for rejection compared with the aviremic (11.3) and low viremic patients (Table 4).

Graft Function

For those patients with functioning graft, the overall mean SCr was 1.5±0.5 mg/dl, and eGFR was 52.1±18.9 ml/min at 1 year post-transplant (Table 4). The transient high viremia and persistent high viremia groups had significantly worse renal function than the control group: SCr (1.85 and 1.75 versus 1.47; \(P=0.01\) and \(P=0.001\), respectively) and lower eGFR (42.1 and 44.9 versus 53.1; \(P=0.01\) and \(P=0.01\), respectively).

Discussion

In the current study, we attempted to investigate the impact of transient versus persistent BK viremia in the context of measured VLs on kidney transplant outcomes. Because there is no universal definition for transient BK viremia, we chose a 3-month interval for viral clearance to reduce the possibility of false positive tests. Because BKV loads \(\leq 10,000\) copies/ml have been suggested as a predictor of BKVAN (1,8–10), we subclassified our population into high and low VLs using a 10,000-copy/ml cutoff. The incidence of BKV viremia in our population during the first year was 21%, which is similar to recent reports ranging from 11.5% to 34.6% (5,8,13). Clinical and epidemiologic factors were comparable among the different groups, including recipient age, sex, race, body mass index, cause of ESRD, panel reactive antibody, type of transplant, source of the kidney, previous transplant, depleting induction, maintenance immunosuppression, and donor age, sex, race, and body mass index (Table 1). We have
recently reported that cytomegalovirus (CMV) viremia is associated with a lower incidence of subsequent BKV infection, presumably because of a reduction in immunosuppression after the diagnosis of CMV viremia (14). However, CMV viremia itself was not significantly different among the five groups in this study ($P=0.80$) (Table 1).

There may be a unique interaction of these two DNA viruses that is both common in renal transplant recipients and displays tropism for kidney tissue (15).

We found that roughly one half of BK viremic patients developed transient viremia lasting for a median duration of 0.65–1.8 months (from onset to clearance). These data imply that viral progression is not universal, and there may be not yet elucidated host defense mechanisms that are capable of viral clearance. This finding is especially true for those patients with low VLs $<10,000$ copies/ml. Seventy patients developed persistent viremia (with low or high VLs). Of these patients, 58.5% ($n=41$) of patients cleared the virus, with a median duration of viremia from 6 (low) to 9 (high) months, respectively. Interestingly, the persistent low viremia group was 3.1-fold more likely to clear the virus compared with the persistent high viremia group (HR, 3.1; 95% CI, 1.5 to 6.5; $P=0.001$). Again, this finding suggests the potential for viral clearance by the host immune system when copy numbers are below a certain threshold, a hypothesis that was also suggested in the work by Schwarz et al. (16).

### Table 4. Transplant outcomes by BKV viremia groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Negative BK Viremia ($n=479$) N (%)</th>
<th>Transient Low Viremia ($n=42$) N (%)</th>
<th>Transient High Viremia ($n=18$) N (%)</th>
<th>Persistent Low Viremia ($n=23$) N (%)</th>
<th>Persistent High Viremia ($n=47$) N (%)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft rejection at any time</td>
<td>103 (21.5)</td>
<td>8 (19)</td>
<td>9 (50)</td>
<td>4 (17.3)</td>
<td>16 (34)</td>
<td>0.01</td>
</tr>
<tr>
<td>Banff score borderline</td>
<td>64 (13.3)</td>
<td>3 (7.1)</td>
<td>3 (16.6)</td>
<td>4 (17.3)</td>
<td>11 (23.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Banff score ≥1A</td>
<td>39 (8.1)</td>
<td>5 (11.9)</td>
<td>6 (33)</td>
<td>0</td>
<td>5 (10.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Treated AcR</td>
<td>52 (10.8)</td>
<td>5 (11.9)</td>
<td>7 (38.8)</td>
<td>2 (8.6)</td>
<td>6 (12.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Graft rejection before BK viremia</td>
<td>N/A</td>
<td>2 (4.7)</td>
<td>2 (11.1)</td>
<td>2 (8.6)</td>
<td>1 (2.1)</td>
<td>0.99</td>
</tr>
<tr>
<td>TCMR</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Graft rejection after BK viremia</td>
<td>N/A</td>
<td>6 (14.2)</td>
<td>7 (38.8)</td>
<td>2 (8.6)</td>
<td>15 (31.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>TCMR</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment method</td>
<td>N/A</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>intravenous steroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Tac/MMF</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rejection rate±SD per 100 patients/yr$^c$</td>
<td>11.3±3.2</td>
<td>10.3±3.1</td>
<td>21.1±4.7</td>
<td>6.7±0.1</td>
<td>17.9±3.8</td>
<td>0.002</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>5.2 to 17.8</td>
<td>4.3 to 16.2</td>
<td>13.1 to 29.1</td>
<td>6.5 to 6.8</td>
<td>10.4 to 25.4</td>
<td></td>
</tr>
<tr>
<td>Time AcR (mo)</td>
<td>Median</td>
<td>7.3</td>
<td>6.4</td>
<td>4.2</td>
<td>6.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Range</td>
<td>0.1–38.8</td>
<td>0.3–14.8</td>
<td>0.5–12.4</td>
<td>0.2–13</td>
<td>1.5–19.5</td>
<td></td>
</tr>
<tr>
<td>SCR (mg/dl)$^b$</td>
<td>Mean/SD</td>
<td>1.47/0.4</td>
<td>1.4/0.2</td>
<td>1.85/0.7</td>
<td>1.46/0.5</td>
<td>1.75/0.6</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.90$^d$</td>
<td>0.01$^d$</td>
<td>0.90$^d$</td>
<td>0.90$^d$</td>
<td>0.001$^d$</td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m$^2$)$^b$</td>
<td>Mean/SD</td>
<td>53.1/19.4</td>
<td>53.3/14.9</td>
<td>42.1/16.1</td>
<td>53.1/19.1</td>
<td>44.9/15.1</td>
</tr>
<tr>
<td>$P$ value</td>
<td>0.90$^d$</td>
<td>0.01$^d$</td>
<td>0.90$^d$</td>
<td>0.90$^d$</td>
<td>0.005$^d$</td>
<td>0.01$^c$</td>
</tr>
<tr>
<td>BKVAN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7 (14.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient survival</td>
<td>461 (96)</td>
<td>38 (90.4)</td>
<td>18 (100)</td>
<td>21 (91.3)</td>
<td>42 (89.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Graft survival</td>
<td>447 (93.3)</td>
<td>35 (83.3)</td>
<td>18 (100)</td>
<td>21 (91.3)</td>
<td>42 (89.3)</td>
<td>0.60</td>
</tr>
<tr>
<td>Death-censored graft survival</td>
<td>465 (97.1)</td>
<td>39 (92.8)</td>
<td>18 (100)</td>
<td>23 (100)</td>
<td>47 (100)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

AcR, acute rejection; TCMR, T cell–mediated rejection; AMR, antibody-mediated rejection; SCR, serum creatinine; BKVAN, BK virus–associated nephropathy.

$^a$Graft rejection rates were calculated from date of transplant until last date of follow-up for the negative BK viremia group and from 3 months after the onset of BK viremia until last date of follow-up for the BK viremia-positive groups.

$^b$Twelve months post-transplant.

$^c$ANOVA test.

$^d$Compared with negative control group using Tukey–Kramer all pairs test.
The persistent high viremia group showed significantly worse 1-year graft function compared with the BK-negative group: SCr (1.75 versus 1.47 mg/dl; \( P = 0.001 \)) and eGFR (44.9 versus 53.1 ml/min; \( P = 0.01 \)) (Table 4). In addition, 100% of BKVAN cases were observed exclusively in patients with persistent high viremia. This finding concurs with the previously believed sequence of evolution of BK reactivation from persistent high viremia to clinical and histologic BKVAN (5,6,9,17). Therefore, identifying BK viremic recipients with persistent VLs>10,000 copies/ml for >3 months is essential to control the number that will go on to BKVAN and graft damage. This definition may capture patients with early high VL who have a clinical picture of presumptive BKVAN (18).

A novel finding in this study was that patients with transient high viremia showed significantly worse 1-year graft function (SCr: 1.85 versus 1.47, \( P = 0.01 \); eGFR: 42.1 versus 53.1, \( P = 0.01 \)), even in the absence of shown histologic BKVAN (negative in situ hybridization) (Table 4). This finding suggests the possibility that mechanisms other than direct tissue invasion by the BK virus may be responsible for graft dysfunction or that sampling error for BK viral particles occurred. Others have suggested that any VL>10,000 copies/ml suggests a presumptive or emerging BKVAN (1,8–10).

We also found that patients with transient high viremia had a 2.9-fold increased risk to develop acute rejection (either at any time or after BKV reactivation) compared with the BKV-negative group (HR, 2.9; 95% CI, 1.3 to 5.4; \( P = 0.01 \)) (Table 4). Some have suggested that this association is caused by a decrease in immunosuppression after the diagnosis of BK viremia. However, we found that mean blood levels of MMF and tacrolimus after detecting BK viremia in the transient viremia groups were not significantly lower compared with the negative control group (\( P = 0.10 \) and \( P = 0.30 \), respectively) (Table 3). This observation may suggest the possible upregulation of host immunity that leads to antidonor responses. The induction of both specific and nonspecific immune reactive cytokines has been observed in transplant patients infected with the BK virus (19,20).

The 36-month patient and graft survival in our study population was 95.2% and 92.6%, respectively. During the study interval, patient and graft survival rates were comparable among the five groups (\( P = 0.10 \) and \( P = 0.60 \)) (Figure 1, Table 4). In the BKV aviremic group, 11 (2.2%) patients died with functioning graft, 7 (1.4%) patients died with a failed graft, and 14 (2.8%) patients returned to dialysis. Among the BK viremic patients, three (all belonged to transient low viremia group) patients lost their graft for causes not related to BKV infection (fungal infection, heart failure, and surgical complications), and 11 patients died with a functioning graft. No death-censored graft losses were observed in the transient high viremia, persistent high viremia, and persistent low viremia groups. Of seven patients diagnosed with BKVAN, one patient died 11 months after transplant because of fungal infection (invasive mucormycosis), with no death-censored graft loss. These results are substantially better than earlier reports in the late 1990s and early 2000s reporting graft loss rates up to 60% after BKVAN (21–24), which may be because of better awareness of the virus as well as early detection and rapid intervention.

Our study does have a number of limitations. Although the results followed a prospective screening protocol, the data analysis was performed in a retrospective fashion, with the inherent limitations of such an approach. The management of recipients with BK viremia included several clinicians and is subject to their best interpretation of clinical events and tests. The use of a commercial laboratory for BK PCR is subject to the reported variations of this assay. As reported, there is a possible 10%–30% false negative rate for in situ hybridization of BKVAN because of sampling error and focal viral invasion (25). The subclassified BKV populations may be underpowered to detect some observations and too small for multivariable modeling of outcomes. Alternatively, the strengths of the study are the relatively large number recipients tested for BKV and the long duration of follow-up. The high BKV screening protocol compliance rate and the large number of transplant biopsies done offer a unique window into the biology of this post-transplant infection. Future studies should focus on the evolution of specific host cellular immune responses to the BKV in the immunosuppressed transplant population.

In conclusion, low VL BK viremia, either transient or persistent, does not have a significantly negative impact on transplant outcomes. Persistent high viremia is associated with a greater risk for BKVAN and subsequent graft dysfunction. Transient high viremia may be associated with poor graft function, even in the absence of BKVAN, suggesting the possibility of an indirect mechanism for allograft injury distinct from direct kidney tissue invasion. This finding suggests that recipients with high BK VLs need close observation, even after clearance of the virus. These data support the role of surveillance for BK viremia in the first year after transplant. Future studies are needed to determine whether targeting of those recipients with persistent high VLs will diminish the impact of this infection on long-term transplant outcomes.

Disclosures

None.

References


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