Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.781232

Duzce Med J, 2020;22(3):180-184
Düzce Tıp Fak Derg, 2020;22(3):180-184

BK Virus Infections in Pediatric Patients with Hematopoietic Stem Cell Transplantation

Hematopoetik Kök Hücre Transplantasyonu olan Pediatrik Hastalarda BK Virüs Enfeksiyonları

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Received / Geliş Tarihi : 24.08.2020
Accepted / Kabul Tarihi : 05.11.2020
Available Online / Çevrimiçi Yayın Tarihi : 25.12.2020

ABSTRACT

Aim: BK virus (BKV)-associated hemorrhagic cystitis (HC) is a common complication in patients after hematopoietic stem cell transplantation (HSCT). The aim of this study was to investigate the incidence of BKV infection in pediatric patients receiving HSCT.
Material and Methods: Total of 51 patients aged between 16 months and 16 years old and followed up between October 2015 and September 2017 were included in the study. The patients were monitored by quantitative real-time polymerase chain reaction (Anatolia Geneworks, Turkey) test for the detection of BKV DNA in urine and blood.
Results: Of patients, 46 received allogeneic HSCT and 5 autologous HSCT. BKV DNA positivity was detected in urine and/or blood of total 27 (52.9%) patients in whom 26 (56.5%) of 46 patients with allogeneic transplantation, and 1 (20.0%) of 5 patients with autologous transplantation. BKV viral load in urine $>10^7$ copies/ml required for preemptive treatment was detected in 12 (26.1%) of 46 patients received allogeneic HSCT. The development of HC was prevented in 9 (75.0%) of the 12 patients given preemptive treatment, while 3 (25.0%) cases developed HC and cured by treatment. BKV viruria was detected $>10^9$ copies/ml in two weeks before the onset of HC and was accepted as a prognostic indicator for predictive diagnosis of HC. BKV viremia was found $>10^4$ copies/ml in 1 patient within two weeks before the onset of cystitis.
Conclusion: Screening for BKV infection, especially BKV viruria in HSCT patients, is recommended for the predictive diagnosis of HC in patients at high risk.
Keywords: BK virus; hematopoietic stem cell transplantation; hemorrhagic cystitis; polymerase chain reaction.

ÖZ

Amaç: BK virus (BKV) ile ilişkili hemorajik sistit (HS), hematopoetik kök hücre transplantasyonu (HKHT) yapılan hastalarda yaygın görülen bir komplikasyondur. Bu çalışmanın amacı, HKHT yapılan çocuk hastalarda BKV enfeksiyonu insidansının araştırılmasıdır.
Gereç ve Yöntemler: Çalışmaya Ekim 2015 ile Eylül 2017 tarihleri arasında izlenen, yaşları 16 ay ile 16 yıl arasında olan toplam 51 hasta dahil edilmiştir. Hastalar BKV DNA'nın idrar ve kanda tespiti için kantitatif gerçek-zamanlı polimeraz zincir reaksiyonu (Anaolia Geneworks, Türkiye) testiyle monitörize edilmiştir.
Bulgular: Hastaların 46'sına allojenik HKHT ve 5'ine otolog HKHT yapılmıştır. Allojenik nakil yapılan 46 hastanın 26'sında (%56,5) ve otolog nakil yapılan 5 hastanın 1'inde (%20,0) olmak üzere toplam 27 (%52,9) hastanın idrar ve/veya kanında BKV DNA pozitifliği saptanmıştır. Allojenik HKHT yapılan 46 hastanın 12 (%26,1)'sinde preemptif tedavi için gereken idrarda $>10^7$ kopya/ml BKV viral yük düzeyi tespit edilmiştir. Preemptif tedavi uygulanan 12 hastanın 9'unda (%75,0) HS gelişmesi önlenirken 3'ünde (%25,0) HS gelişmiş ve tedaviyle iyileşmiştir. HS gelişmeden önceki iki hafta içinde BKV virurisi $>10^9$ kopya/ml olarak tespit edilmiş ve HS prediktif tanısı için prognostik bir gösterge olarak kabul edilmiştir. BKV viremisi 1 hastada sistit gelişmesinden önceki iki hafta içinde $>10^4$ kopya/ml olarak tespit edilmiştir.
Sonuç: Yüksek riskli hastalarda HS prediktif tanısı için BKV enfeksiyonu, özellikle HKHT hastalarında BKV virüri taraması önerilir.
Anahtar kelimeler: BK virüs; hematopoietik kök hücre transplantasyonu; hemorajik sistit; polimeraz zincir reaksiyonu.

INTRODUCTION

Hemorrhagic cystitis (HC) associated with BK virus (BKV) is a common complication in patients with hematopoietic stem cell transplantation (HSCT). BKV is a small (40-45 nm), non-enveloped DNA virus with icosahedral capsid and circular double-stranded genome, belonging to the Polyomaviridae family. BKV was first isolated by Gardner in 1971 from the urine sample of a renal transplant patient who developed ureteral stenosis and acute renal failure and it was named BKV according to the patient's initials. BKV infections are very common worldwide and more than 90% of adults are seropositive. BKV primer infection typically occurs during early childhood, before 10 years, often at age 4-5 years. Primary BKV infections are usually asymptomatic or mild upper respiratory tract infections. BKV is transmitted mainly by the respiratory route. After primary infection, viremia develops and BKV spreads to (infects) many different organs and enters latent phase. BKV remains latent especially in the uroepithelial cells of the kidney and urinary tract. BKV does not cause disease in immunocompetent healthy individuals in the latent phase but occasionally reactivates and manifests itself as asymptomatic viruria. However, the disease will develop in the case of immunodeficiency or in transplant recipients who undergo immunosuppressive treatment, primarily in kidney or bone marrow transplant patients. Serious complications of BKV reactivation are HC in allogeneic HSCT recipients and nephropathy that develops most commonly in renal transplant recipients. BKV may also lead to asymptomatic hematuria, ureteral stenosis and nephropathy in patients with HSCT. BKV infection is common in patients after allogeneic HSCT, but rarely seen in autologous HSCT patients. HC is an important complication after HSCT. HC is divided into two types based on the onset time of cystitis in patients with allogeneic HSCT. Early onset HC develops in the pre-engraftment period during the conditioning regimen, especially within 48-72 hours after the initiation of conditioning regimen or within 1 week of transplantation. It is caused by the direct toxicity of chemotherapeutic drugs such as cyclophosphamide and busulfan used in the conditioning regimen or of the pelvic radiation to the urothelial mucosa. In the post-engraftment period, factors such as viral infections and acute graft versus host disease (GVHD) are responsible for late-onset HC occurring. BKV is the major cause of late-onset HC after allogeneic transplantation. BKV-associated HC occurs between 2 and 8 weeks (1 week to 6 months) after transplantation. The incidence of BKV-associated HC after allogeneic HSCT is 13% on average. The rate of BKV-associated HC is 18% (8-25%) in children with allogeneic HSCT, and 16% (7-54%) in adults (1). The aim of this study was to investigate the incidence of BKV infection in children with HSCT.

MATERIAL AND METHODS

A total of 51 pediatric patients aged between 16 months and 16 years, who underwent HSCT (46 allogeneic and 5 autologous,) between October 2015 and September 2017, were prospectively studied. Patients were informed for consent. The study protocol was approved by the Institutional Ethics Committee of Cukurova University (dated 13.05.2016 and numbered 53/7). Thirty-one male and 20 female patients, aged between 16 months and 16 years, were included in the study. The patients were randomly divided into 5 groups according to their age (Table 1). Other demographic and clinical characteristics of the patients are also shown in Table 1 and, information about donor gender and type, transplant type, stem cell source and complications are shown in Table 2. Conditioning regimen was applied to patients for approximately 10 days before HSCT. Of the 51 patients, 36 (70.6%) received myeloablative treatment (29 cyclophosphamide and busulfan, 4 cyclophosphamide, ATG, fludarabine and busulfan, and 3 cyclophosphamide, fludarabine and busulfan), and 15 (29.4%) received low-density treatment (13 of the patients received cyclophosphamide, ATG and fludarabine, and 2 cyclophosphamide). Patients were followed up one week prior to transplantation, one per week for first 3 months after transplantation, and one every month up to 1 year after transplantation for BKV viruria and viremia. The extraction of viral DNA from urine and plasma samples was performed with Magnesia Viral Nucleic Acid Extraction Kit EP (Geneworks Anatolia, Turkey). The Bosphorus BKV quantification kit v1 (Anatolia Geneworks, Turkey) was used for detection of BKV DNA in urine and blood samples. For each patient sample, 10 µl of the sample DNA extract was added to the mixture consisting of 14.9 µl BKV master mix and 0.1 µl internal control (IC). Positive and negative controls were included in each study. Amplification was performed in a Qiagen Montania 4896 real-time polymerase chain reaction (PCR) instrument according to the manufacturer's protocol as 1 cycle of 14:30 min at 95 °C (first denaturation), and 50 cycles of 30 seconds at 97 °C (denaturation) and 90 seconds at 53 °C (annealing and synthesis), following the manufacturer's protocol.

All patients with allogeneic HSCT received cyclosporin and methotrexate for GVHD prophylaxis. Prophylactic acyclovir treatment was given to all transplant patients for 90 days. In addition Prophylactic intravenous immunoglobulin (IVIG) was used (0.5 gr/kg) on the day before transplantation and on day 5 after transplantation in 23 of 46 patients with allogeneic HSCT. Preemptive reduction of immunosuppression was started in patients with high-level BKV viruria (viral load $>10^7$ copies/ml) HC was treated with cidofovir, oral levofloxacin, platelet transfusion and bladder irrigation according to the clinical condition of the patient.

Statistical Analysis

Descriptive statistics were given as mean±standard deviation for numerical variables. Categorical variables were summarized with frequencies and percentages.

RESULTS

The ages of 51 patients included in the study were between 16 months and 16 years. The mean age of the patients was 6.9±4.4 years. 31 (60.8%) of the patients were male and 20 (39.2%) were female. Twenty-seven (52.9%) of 51 patients had BKV DNA positivity in their urine and/or blood. Twelve patients (23.5%), with urine BKV DNA levels above $>10^7$ copies/ml who required for preemptive treatment, were in allogeneic HSCT group (26.1%, 12/46).

In addition, BKV viremia was detected in 6 (13.0%, 6/46) of these 12 patients, and 4 of these 6 patients (8.7%) has a viral load >10^4 copies/ml. In 27 patients with BKV DNA positivity, the mean initiation time of viruria was 9.4±9.7 weeks (1st week to 12th months) while in 12 patients with a viral load of more than 10^7 copies/ml, the mean time to onset of high-level BKV viruria was 6.1±8.4 weeks (1st week to 7th months).

Three of 51 patients had HC median 56 (55-61) days after transplantation and all were in the allogeneic HSCT group (6.5%, 3/46). HC developed in 1 (7.1%, 1/14) of 5 patients who received a low-density treatment regimen and had a viral load >10^7 copies/ml. HC developed in 2 (6.2%) of 7 patients with high-level viruria who underwent myeloablative regimen. Data about the treatment regimens are given in Table 3.

The presence of BKV DNA in urine and/or blood was investigated before transplantation. It was found positive in 4 (7.8%) patients and only in urine (<10^7 copies/ml). In 2 (50.0%) of these patients, the viral load of urine BKV DNA was >10^7 copies/ml and preemptive treatment was applied to these patients. During the follow-up, viremia developed once in these 2 patients and the blood viral load of BKV DNA was determined as $2.8x10^3$ copies/ml and $6.0x10^2$ copies/ml, but HC was not developed. On the other hand, in 10 (21.3%) of 47 patients with BKV DNA negativity in urine and/or blood before transplantation, had BKV DNA viral load >10^7 copies/ml after transplantation.

Twelve (26.1%) of 46 patients who receipt allogeneic transplantation developed GVHD, 8 (17.4%) of them were acute and 4 (8.7%) were chronic GVHD. In 5 (62.5%) of 8 patients who developed acute GVHD, the viral load of urine BKV DNA was >10^7 copies/ml. High-level viremia was detected in only 7 (18.4%) of 38 allogeneic HSCT patients who did not develop acute GVHD, and acute GVHD is seen as a risk factor for BKV infection.

Prophylactic IVIG was given to 23 patients who underwent allogeneic stem cell transplantation. Five (21.7%) of these patients had high-level viruri and only 1 (4.3%, 1/23) had HC. In 7 (30.4%) of 23 patients who were not given IVIG, the viral load in urine was >10^7 copies/ml and HC was observed in 2 (8.7%) patients.

HC was seen in 3 (25.0%) of 12 patients who received preemptive therapy and all of these patients had urinary BKV DNA viral load >10^9-10^{11} copies/ml in 2 weeks prior to the development of HC, whereas only 1 patient had >10^4 copies/ml BKV viremia. With preemptive therapy, the development of HC was prevented in 9 (75.0%) of 12 patients.

Eight patients died in the study group, 1 of them died by GVHD and pneumonia, 3 of them by GVHD and 4 of them had died by other reasons. As a result, none of the patients who was underwent HSCT died due to BKV infection.

DISCUSSION

After primary infection, viremia develops and BKV passes into latent phase by spreading into many organs. BKV remains latent in the kidney and uroepithelial cells in particular. In healthy individuals, asymptomatic BKV viruria can be seen in the latent phase. In the other hand, BKV causes severe complications such as nephropathy in patients with bone marrow and kidney transplantation and receiving immunosuppressive therapy. Approximately 90% of the general population is infected with BKV. BKV infections are usually seen in early (<10 years) childhood (2). BKV infections in transplant recipients commonly are

Table 1. Demographic and clinical features of patients, n (%)

Gender, n (%)	
Male	31 (60.8)
Female	20 (39.2)
Age, n (%)	
0-2 years	9 (17.6)
3-5 years	15 (29.4)
6-10 years	15 (29.4)
11-15 years	9 (17.6)
16-18 years	3 (5.9)
Preparation regimen, n (%)	
Myeloablative regimen	36 (70.6)
Low-density regimen	15 (29.4)
Diagnosis, n (%)	
Fanconi aplastic anemia	9 (17.6)
Thalassemia major	18 (35.3)
Acute myeloid leukemia	2 (3.9)
Acute lymphoblastic leukemia	3 (5.9)
Hodgkin lymphoma	1 (2.0)
Chronic granulomatous disease	1 (2.0)
Severe combined immunodeficiency	3 (5.9)
Non-Hodgkin's lymphoma	2 (3.9)
Neuroblastoma	4 (7.8)
Diamond Blackfan anemia	1 (2.0)
T-cell lymphoma	1 (2.0)
Sickle cell anemia	2 (3.9)
Ewing sarcoma	1 (2.0)
Myelodysplastic syndrome	1 (2.0)
Aplastic anemia	1 (2.0)
Hemophagocytic lymphohistiocytosis	1 (2.0)

Table 2. Donor gender and type, transplant type, stem cell source and complications, n (%)

Transplant type	
Allogeneic	46 (90.2)
Autologous	5 (9.8)
Donor gender (n=46)	
Male	24 (52.2)
Female	22 (47.8)
Donor type (n=46)	
HLA compatible relative	44 (95.7)
HLA compatible unrelated	2 (4.3)
GVHD (n=46)	
Absent	34 (73.9)
Acute GVHD	11 (23.9)
Chronic GVHD	1 (2.2)
Stem cell source	
Bone marrow	39 (76.5)
Peripheral blood stem cells	11 (21.6)
Cord blood and bone marrow	1 (2.0)
Complications	
Fever	30 (58.8)
Gastroenteritis	20 (39.2)
Skin rash	16 (31.4)
Oral mucositis	14 (27.5)
Renal dysfunction	1 (2.0)
Hemorrhagic diathesis	3 (5.9)
Cystitis	3 (5.9)
Liver dysfunction	6 (11.8)
Pneumonia	1 (2.0)
Hematuria	3 (5.9)
Organomegaly	8 (15.7)

GVHD: Graft versus host disease

Table 3. Transplant type, treatment regimen and viral load distribution of urine BKV DNA of patients, n (%)

	Myeloablative Regimen (n=36)			**Low-Density Regimen (n=15)**		
	BKV DNA $<10^7$ copy/ml	**BKV DNA $>10^7$ copy/ml**	**BKV DNA (+)**	**BKV DNA $<10^7$ copy/ml**	**BKV DNA $>10^7$copy/ml**	**BKV DNA (+)**
Allogeneic	10 (27.7)	7 (19.4)	17 (47.2)	4 (26.7)	5 (33.3)	9 (60.0)
Autologous	-	-	-	1 (6.7)	0 (0.0)	1 (6.7)
Total	10 (27.7)	7 (19.4)	17 (47.2)	5 (33.3)	5 (33.3)	10 (66.7)

seen in genitourinary tract in consequence of BKV's genitourinary epithelium tropism. In bone marrow transplant patients, BKV viruria is associated with various clinical manifestations such as asymptomatic hematuria, HC, ureteral stenosis and interstitial nephritis. In the case of immunosuppression, BKV reactivation is observed and according to the studies, BKV viruria is 40-87% and its viremia is 17-67% (3,4). In patients undergoing chemotherapy treatment after HSCT and solid organ transplantation, the immune system is suppressed and as a result, the virus reactivates and may cause HC (5,6). HC is characterized by hematuria due to inflammation of the bladder mucosa. Accompanying symptoms are dysuria, frequent urination and suprapubic pain (2). HC has been reported as 6.5-25% in patients who underwent HSCT and it is associated with high morbidity and mortality. BKV viruri is usually seen in 2 to 8 weeks after HSCT and continues for 1 week to 2 months. In many studies, it has been reported that high viral load in urine is a sign of HC. In particular, the viral load $>9.0x10^6$ copies/ml in the urine and $>10^4$ copies/ml in the blood are risk indicators for the development of HC. Deaths also have been reported because of BKV associated HC.

Other important risk factors associated with the development of HC except BKV infection; incompatible donor, high intensity preparation regimen (anti-thymocyte globulin, cyclophosphamide, busulfan), acute GVHD, age and radiotherapy (7,8).

In our study; high-level viruri ($>10^7$ copies/ml) were detected in 12 (26.1%) of 46 patients who underwent allogeneic transplantation. BKV DNA positivity in urine before transplantation urinary and acute GVHD were seen as risk factors for the development of high-level BKV viruri. BKV viruria with $>10^7$ copies/ml levels in patients with and without acute GVHD were 62.5% and 18.4%, respectively. The presence of acute GVHD was identified as a risk factor for the increase of BKV DNA viral load to the level requiring preemptive therapy.

BKV DNA was positive ($<10^7$ copies/ml) before transplantation in 4 of 51 patients who underwent HSCT. Viruria (BKV DNA viral load $>10^7$ copies/ml) and viremia ($<10^4$ copies/ml) were detected in 2 (50.0%) of 4 patients. Of 47 patients with BKV DNA negativity before transplantation, 10 (21.3%) patients had BKV DNA viral load $>10^7$ copies/ml after transplantation, with a lower rate. Pre-transplant BKV viruri positivity is considered to be a risk factor for increased levels of viral load requiring preemptive treatment and for the development of high-level BKV viruri. The rate of viruri in 51 patients who underwent HSCT was 52.9% and is close to 50% rate of Bogdanovic et al. (9). The BKV viruri rate in allogeneic HSCT patients was 56.5% and was close to other studies (8,10-13).

Urinary viral load was $>10^7$ copies/ml and preemptive treatment was applied in 12 (26.1%) of allogeneic HSCT patients. HC developed in 3 of the patients who had preemptive therapy. Two weeks before the occurrence of HC, $>10^9$ copies/ml of the BKV virus was a risk indicator. Hayden et al. (7) similarly found the BKV viruri as $>10^9$ copies/ml at the time of 13 days before HC. Other studies have also detected BKV viruri at $>10^6$-10^{10} copies/ml in the 2-13 days before HC (9,11,14-16).

In our study, only 1 of 3 HC cases was found to be BKV viremia $>10^4$ copies/ml in 2 weeks prior to the development of cystitis and it is same with the results of Oshrine et al. (11) and Lee et al. (17) On the other hand, other studies reported levels of $>10^{2\text{-}6}$ copies/ml (13,14,16).

The rates of BKV viruri ($>10^7$ copies/ml) according to our study were lower in the myeloablative group (19.4%) than low-density regimen group (33.3%), while Giraud et al. (13) found it higher in the myeloablative group (30%) than low-density regimen group (19%). In addition, in our study, HC in patients with myeloablative and low-density treatment regimen was similar with 5.5% and 6.7%, respectively, while Giraud et al. (16) detected the incidence of HC as higher in the myeloablative group (78%) than the low-density regimen group (22%).

In this study, 62.5% of patients with acute GVHD had a viral load $>10^7$ copies/ml and this rate was 18.4% in patients without acute GVHD. This rate was 67% and 50% in the studies of Bogdanovic et al. (9) and Hayden et al. (7), respectively. They declared acute GVHD as a risk factor for BKV infection.

The rate of HC was 6.5% in allogeneic HSCT patients and it is close to 9% rate of Kwon et al. (15) and 8.9% rate of Lee et al. (17), and similar with 6% rate of Mori et al. (18), but lower than the other studies (7,10,11,19,20).

According to our results, HC occurred median 56 days after HSCT and it is close to result of Lee et al. (18, 69 days). But the many other studies reported that HC developed in a shorter time (12,14,15,19-21).

CONCLUSION

In conclusion, in all 3 cases with HC, the viral load in the urine was 10^9 copies/ml in the 2 weeks prior to the development of HC, and this finding was a prognostic marker for the development of HC. Early detection of viral infections will be effective in preventing the progression of the disease by providing timely initiation of preemptive therapy with the monitoring of BKV viral load in patients with HSCT. More prospective studies in the future for predictive diagnosis and preemptive therapy of BKV-associated HC may help to reduce the complications and mortality associated with transplantation in HSCT recipients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Çukurova University Faculty of Medicine (13.05.2016, 53/7).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgements: None declared by the authors.

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