RISK FACTORS AND CLINICAL CHARACTERISTICS OF BK POLYOMAVIRUS INFECTION AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

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Abstract

Backgraund: BK polyomavirus (BKPyV) infections are an important cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). Hemorrhagic cystitis (HC) may occur in patients undergoing HSCT due to the BKPyV reactivation. The aim of this study was to assess risk factors, clinical characteristics and treatment options of BKPyV infections after HSCT.

Methods: Study was conducted at the adult HSCT units of a University Hospital which is a tertiary care centre in Central Turkey from January 2017 to December 2019.

Results: A total of 54 patients with HSCT were retrospectively evaluated and BKPyV disease was found in 24 (44%). HC was seen in 20 (83%) of patients with BKPyV disease . The median age of patients was 42 and 50% of them were male. The most common underlying disease was Acute Myeloid Leukemia (62%). Five patients had autologous and 15 patients had allogeneic HSCT. The median time to engraftment was 15 days. GVHD was seen only in 7 patients. The median time elapsed to BKPyV disease after HSCT was found as 60 days. Nineteen patients with BKPyV disease had grade 3 and one patient had grade 2 HC. While

BKPyV viremia was positive in five patients, viruria was detected in all patients. Eighteen (75%) of the patients with BKPyV disease were treated with cidofovir (5mg/kg IV) and 11 with ciprofloxacin (800 mg/day). Four of the patients who received intravesical cidofovir (dose). The complete response was obtained 53% of patients with BKPyV disease .

Conclusion: BKPyV disease is an emerging clinical problem after HSCT causing morbidity and mortality. It can develop especially in the early period after allogeneic stem cell transplantation. This situation has been associated with the use of immunosuppressive treatments after transplantation. Close monitoring of BK virus in high-risk patients can be an important method to improve the complication in the early period.

What is already known about this topic? What does this article add?

BKPyV disease is one of the infections that develop after allogeneic stem cell transplantation. Especially, the use of immunosuppressive agents for the prevention of GVHD is associated with this situation. It may develop in the early period after allogeneic stem cell transplantation. In our study, it was also found to be associated with CMV infection that developed after allogeneic stem cell transplantation. Although cidofovir treatment, which is one of the agents that can be used for the treatment of this infection, is widely used, clinical response rates were found to be low. Therefore, the main purpose of treatment is to reduce the dose of immunosuppressive agents. Close monitoring of the BK virus in high-risk patients may also be an important method to cure early complications.

RISK FACTORS AND CLINICAL CHARACTERISTICS OF BK POLYOMAVIRUS INFECTION AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

INTRODUCTION

BK virus, one of the thirteen known polyomavirus types, is an important cause of morbidity and mortality in haematological patients after hematopoietic stem cell transplantation (HSCT). It was first isolated from urine specimen of renal transplant patient

in 1970 (1,2). BK polyomavirus (BKPyV) associated infection is acquired in childhood and the virus becomes latent in urothelial epithelial cells. Whenever the immune system suppressed, the virus may reactivate and damage the urothelial mucosa causing bleeding resulting in ureteral stenosis, nephropathy and more commonly, hemorrhagic cystitis (1,3). Especially, after HSCT the infection present with asymptomatic viruria or hemorrhagic cystitis (HC). Recent studies have reported, HC was seen approximately 5-25% after HSCT (4). Several risk factors like immunosuppressive drugs, allogeneic transplantation, development of graft versus host disease (GVHD), BK virus serology before transplantation may contribute to thedevelopment of HC. While early-onset HC can be seen the first week after HSCT, late-onset HC can be seen 2 week-6 months after transplantation (1,5). There is not standard treatment of BKPyV associated HC. Generally, reducing immunosuppression is recommended in the absence of GVHD. Cidofovir (intravesical or intravenous), ciprofloxacin, leflunomide are among drugs used in the treatment of BKPyV infection after HSCT (5,6). The aim of the study was to assess risk factors, severity, clinical characteristics and treatment options of BK virus-associated infection in patients with hematological malignancies after HSCT.

MATERIALS AND METHODS

This retrospective study was conducted at the adult HSCT units of the Erciyes University Hospital which is a tertiary care centre in Central Turkey from January 2017 to December 2019. These units have 35 hematopoietic stem cell transplantation beds. The study included all ≥18 years in hematological cancer patients who underwent HSCT and with BK viremia or viruria after HSCT. In addition, patients who underwent HSCT and didn’t develop BK virus disease formed the control group. For risk factor analysis demographic and

clinical characteristics data obtained from patients' medical reports. Data included age, gender, primary malignancy that required HSCT, type of transplantation, using of immunosuppressant, development GVHD, days to engraftment, presence of hematuria or hemorrhagic cystitis, BKPyV PCR level of urine and blood, drugs used for treatment of BK virus infection (supportive or drugs), development of Cytomegalovirus (CMV) reactivation, drugs used for treatment of CMV infection and mortality.

There are different regimens for allogeneic and autologous stem cell transplantation for patients in the pre-transplantation period. BEAM (Karmustin, Etoposide, Cytarabine, Melphalan) chemotherapy protocol is applied to patients 7 days before autologous SCT in transplantation unit. Also, the chemotherapy regimen containing Gmsitabine, Fludarabine, Melphalan, Methotrexate, Cyclosporine is used to patients who underwent Allogeneic SCT from the seventh day before to the sixth day after the stem cell transplantation. These immunosuppressive treatments before transplantation increase the risk of BKPyV reactivation. Also, patients have received GVHD prophylactic regimens, including combinations of some drugs like glucocorticoids, cyclosporine, mycophenolate mofetil (MMF), tacrolimus and methotrexate.

Definitions

BKPyV virus disease was defined as the detection of BKPyV by PCR testing in association with genitourinary symptoms. The diagnostic triad of BKPyV–HC was defined according to ECIL guideline; clinical symptoms of cystitis like abdominal pain and dysuria, grade 2 or higher haematuria, BK viruria with viral loads of > 7 log 10 copies/mL. Also, plasma viral loads of BK virus can be 3-4 log 10 copies/mL. The severity of haematuria is described like grade 1 (microscopic haematuria), grade 2 (macroscopic haematuria), grade 3

(clots and macroscopic haematuria), grade 4 (grade 3 with renal failure to urinary obstruction) (1,7). The cidofovir related nephrotoxicity was assessed by creatinine clearance estimated by the Cockcroft and Gault formula, before the first dose and after the last dose of cidofovir (5).

Routine approach for patients undergoing HSCT: All patients undergoing allogeneic SCT received quinolone for opportunistic bacterial infections, after transplantation until to neutrophil engraftment. If hematuria is confirmed we start hyperhydration. There is no routine screening for BK virus if no etiologies were found for patients with hematuria or urinary symptoms, virus analysis was performed (urine or blood). Also, bladder irrigation and cidofovir 3-5 mg/kg/week IV or intravesical with probenecid were used (1). Complete clinical response was defined as improving the hematuria symptoms completely, partial response as downgrading of hematuria) and failure as worsening hematuria or no changes in urinary symptoms (1,4).

GVHD is a complication that occurs in the patient after stem cell transplantation from both related and unrelated donors. Patients were followed up for GVHD in the first 100 days after transplantation for oppotunistic infections?. They were evaluated for clinical symptoms such as intestinal symptoms (nausea and diarrhea), skin rash, and liver problems. Primary treatments for GVHD are used in our haematology and transplantation unit, including immunosuppressive drugs, corticosteroids, immunosuppressive drugs (cyclosporine, methotrexate, etc.). These treatments are started 60 to 100 days after transplantation and discontinued 6 to 9 months after transplantation without GVHD. Engraftment day was defined as the first of three consecutive days of an absolute neutrophil count >500 cells/µL (8). Virological tests: BKPyV DNA PCR testings of plasma and urine were performed at the

Virology department of clinical microbiology laboratories using a real-time quantitative PCR assay. Urine and plasma ranges of 50-9*10^7 copies/mL.

Viral DNA was extracted by Qiasymphony DSP Virus/pathogen Kit (Hilden, Germany), and viral load was detected by using artus BK virus QS-RGQ Kit (Hilden, Germany) with the real-time polymerase chain reaction method in a Rotor-Gene Q (Hilden, Germany).

Statistical analysis was performed using SPSS software version 22.0 (IBM, Armonk, NY). The chi-square or Fischer exact test was used for categorical variables. The Mann-Whitney U test was used to compare the differences between the two groups. Univariate and multiple binary logistic regression analyses (backward wald) were performed to analyze the effects of variables (confidence interval, CI 95%). In the multiple logistic regression analysis, the variables found to be significantly associated with BK virus infection in the univariate analysis were included. The level of significance was set at $P < 0.05$ for all tests.

Ethics; this research was approved by the Non-invasive Clinical Research Ethics Committee of Erciyes University (Date 15.01.2020, Number 96681246).

RESULTS

A total of 54 patients with HSCT were evaluated during study period and BKPyV disease occurred in 24 (44%) of these patients. The median age was 42 (range, 20 to 68), 50% were male. The most underlying disease was Acute Myeloid Leukemia (62%). Five (20.8%) patients had autologous and 19 (79.2%) patients had allogeneic SCT. The median interval between stem cell transplantation and BKPyV disease onset was 2 months (range, 1 to 15). The median time to neutrophil engraftment was 15 days (range, 9 to 30). Patient characteristicwith or without BK virus disease) are summarized in Table 1. GVHD was seen in fourteen patients. GVHD was developed in fourteen patients (71% skin, 21% gastrointestinal

and 7% liver respectively) and all diagnosed by biopsy. The most common GVHD prophylaxis administered for BK virus disease group was cyclosporine (CSA) (79%), methotrexate (MTX) (71%), glucocorticoid (62%) followed by mycophenolate mofetil (MMF) (46%).

CMV reactivation was detected in 13 (54%) of patients with BK virus disease and four (13%) of patients with non-BK virus disease. Among the patients with BKPyV disease, five patients received ganciclovir intravenous IV (5 mg/kg/gün bid), 5 patients received cidofovir IV and 3 patients received cidofovir plus ganciclovir treatment. Treatment response was seen only in 12 patients, but no response in one patient receiving cidofovir IV treatment.

HC was documented in 20 (83%) of patients after HSCT. None of the patients had a haemorrhagic urine. Nineteen patients (79%) with BKV disease had grade-3, 4 patients (17%) had grade-1 and only one patient (4%) had grade-2 haematuria. The median time elapsed to BK virus disease after HSCT was 60 days (range, 30 to 450). While BK viremia was positive in five patients (21%), viruria was positive for all patients. The majority of patients were received supportive treatment including hydration. The urinary catheter was inserted for bladder irrigation to patients with microscopic hematuria or use of intravesical cidofovir. In patients with BKPyV disease, 9 (37%) patients with cidofovir, 3 (12%) patients with ciprofloxacin, 9 (37%) patients were treated with ciprofloxacin plus cidofovir (5 mg/kg/gün twotimes of week) combination. Characteristics of BKPyV infection and Stem Cell Transplant patients with and without hemorrhagic cystitis are listed in Table 2. Twelve (50%) of them was treated by intravenos cidofovir, 4 (17%) patients intravesical cidofovir and 2 (8%) patients were treated by IV plus intravesical cidofovir combinations therapy. BKPyV related HC patients received 0.5-1 mg/kg intravenous cidofovir once every two weeks due to the persistence of hematuria. Bladder irrigation was performed in approximately 3 (12%)

patients who were followed up for hematuria without symptomatic HC. Only one patient was while receiving cidofovir therapy.developed renal function abnormalities or had renal failure

After treatment of BKPyV-related HC, 10 (55%) patients achieved a complete response to the viruria or viremia and 9 patients achieved no response. Probenecid dose oral preparation has administered before therapy for patients treated with intravenous cidofovir. During the study period, 9 (37%) of 24 patients with BKPyV disease died.

Univariate analysis revealed that CMV reactivation and the use of immunosuppressive agents (corticosteroids, methotrexate, mycophenolate mofetil, cyclosporine) for GVHD prophylaxis were significantly associated with BKV-related HC. In multivariate analysis, only GVHD prophylaxis regimen like corticosteroids, methotrexate, MMF, cyclosporine was found the significant risk factor for BKV-related HC (hazard ratio 10.93, 95% Cl 2.6-45.7, p=0.001).

DISCUSSION

We examined the clinical risk factors for BK virus infection after SCT. In recent years, BKV-HC cases have started to appear together with the increase in allogeneic stem cell transplants and immunosuppressive therapy in patients with haematological malignancies (1,2,4). The overall incidence of BKV-HC is reported at 5%-68% (1,2).

In recent studies, Hu *et al*. reported 21% BK virus disease, 18% HC among 38 HSCT recipients. Lunde et al. were reported that in 1321 allogeneic transplant patients, HC developed 219 (17%) at a median of 22 days after alloHCT (9,10). In another study of 102 allo-SCT patients, HC occurred in 25%, BKV was identified in 80% of patients (11). In our study BKV was identified in 44% of 54 patients, HC occurred in 19 of patients (79%) with

BK virus infection. Although small number of cases, our incidence rates are higher than other studies, which is thought to be due to the fact that HC is a frequent complication after allogeneic stem cell transplantation and the increases of stem cell transplantation and intensive immunosuppressive treatments in our centre.

Patients who develop acute GVHD are treated frequently with immunosuppressant drugs and high doses of systemic corticosteroids. The presence and agents used for the treatment of GVHD may be a risk factor for infections. Many previous studies have reported an association between BK virus infection and immunosuppressive treatment. Immunosuppression resulting from GVHD itself and the effects of these medications causes an increased risk of HC by causing BKPyV replication and uroepithelial damage (1,7,8). In the study conducted by Park Hoon *et al*. 18 of 69 allo-SCT patients had BK associated HC, and 9 of them had acute GVHD. It was observed that only 7 patients received antithyroglobulin immunosuppression therapy for in vivo T cell depletion. Immunosuppressive therapy was followed up in low-risk BKV-HC patients without evidence of GVHD, whereas in patients with high-risk BKV-HC, immunosuppression was reduced or discontinued due to the risk of GVHD. At the end of the study, acute GVHD was found to be an independent risk factor associated with BK virus infection (4). However, in our study, although GVHD was seen in 14 of patients (of all, 71% had skin, 21% gastrointestinal and 7% liver GVHD, respectively), it was not found as a significant HC-related clinical variable. The most common agents used for GVHD prophylaxis (administered for BK virus disease group) were cyclosporine (CSA) (79%), methotrexate (MTX) (71%), glucocorticoid (62%) followed by mycophenolate mofetil (MMF) (46%).

The use of immunosuppressive agents for GVHD prophylaxis was associated with high-risk factors of developing BKV-related HC in univariate analysis and in multivariate

analysis, GVHD prophylaxis regimen was found significant risk factor. Therefore, according to the patient's BK virus risk status and GVHD grade, blood concentration level of immunosuppressive agent can be monitored and if necessary dose modification should be done (1,7). Some studies have associated HC with CMV reactivation, suggesting that DNA viruses such as CMV can induce BK virus replication in patients underwent allogeneic transplantation. They have demonstrated that reactivation of the BK virus is very important in the development of HC after SCT. BK virus could be detected in the urine after recovery as has been reported in the literature (12) On the other hand, T cell depletion of bone marrow before transplantation was significantly associated with polyomavirus and CMV reactivation (13). In our study, it was observed that CMV infections were more common in BK virus-infected patients and were statistically significant. CMV is inducing BK virus-associated HC, in this respect, treatment with ganciclovir can be suggested that can control CMV infection and lead to reduce HC.

Treatment options for BK-HC in are predominantly supportive therapy. Bladder irrigation, hydration can be used for the treatment of the urothelial damage. Cidofovir, an antiviral agent, ciprofloxacin and leflunomide have also demonstrated activity against BK virus. The major limitation for the use of cidofovir is its nephrotoxicity. In the previous studies, the clinical response rate was 60-100% and toxicity was reported in 9-50% of patients (1,5). Regarding literature and our study cidofovir seems to be efficient, although toxic, treatment for BK-HC (1,5,14). In our study, cidofovir treatment was used in 17 of 19 patients with HC, but nephrotoxicity was developed only in one and the clinical response rate was 52%, the mortality rate was 37% for all patients. In recent studies, Lee *et al*. reported a clinical response rate of patients who were treated with cidofovir as 87%, toxicity rate as 38%. Cesaro *et al*. reported complete clinical response rate 67%, urinary clearance

was 20% in patients with grade 3–4 HC. The failure and partial response of cidofovir were found associated with increased BKV load (15,16). In our study, it was observed that patients with high urinary viral load and HC, despite cidofovir treatment, had lower complete response rates compared to patients with low viral load and not developing HC. However, it was not statistically significant.

In conclusion, BKPyV disease is an emerging clinical problem after HSCT causing morbidity and mortality. BK virus disease is highly associated with CMV infection. It can develop especially in the early period after allogeneic stem cell transplantation. This situation has been associated with the use of immunosuppressive treatments after transplantation. The main goal of treatment is to reduce the dose of immunosuppressive agents. Close monitoring of BK virus in high-risk patients can be an important method to improve the complication in the early period. However, large prospective randomized and well-controlled studies are needed due to the low number of cases.

What is already known about this topic?

What does this article add?

BKPyV disease is one of the infections that develop after allogeneic stem cell transplantation. Especially, the use of immunosuppressive agents for the prevention of GVHD is associated with this situation. It may develop in the early period after allogeneic stem cell transplantation. In our study, it was also found to be associated with CMV infection that developed after allogeneic stem cell transplantation. Although cidofovir treatment, which is one of the agents that can be used for the treatment of this infection, is widely used, clinical response rates were found to be low. Therefore, the main purpose of treatment is to reduce the dose of immunosuppressive agents. Close monitoring of the BK virus in high-risk patients may also be an important method to cure early complications.

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Table 1. Characteristics of Stem Cell Transplant patients with and without BK Polyomavirus

Characteristics	**BK virus disease** (n= 24)	**Non BK virus disease** (n= 30)	*p*	**Multivariate analysis OR (95% CI)**
Age, median (min-max)	42 (20-68)	42 (19-65)	0.875	
Male gender, n (%)	12 (50.0)	20 (66.7)	0.270	
Primary disease, n (%)				
Acute Myeloid Leukemia	15 (62.5)	11 (36.7)	0.099	
Myelodysplastic Syndrome	2 (8.3)	3 (10.0)	0.999	
Multible Myeloma	1 (4.2)	6 (20.0)	0.117	
Acute lymphoblastic Leukemia	3 (12.5)	4 (13.3)	0.999	
Lymphoma	3 (12.5)	6 (20.0)	0.715	
Stem cell transplantation, n (%)				
Autologous	5 (20.8)	9 (30.0)	0.540	
Allogeneic	19 (79.2)	21 (70.0)		
Hemorrhagic cystitis, n (%)	20 (83.3)	0 (0.0)	**0.001**	
Hematuria, Grade, n (%) Grade 1 Grade 2 Grade 3 Grade 4	 4 (16.7) 1 (4.2) 19 (79.2) 0 (0.0)	 2 (100.0) 0 (0.0) 0 (0.0) 0 (0.0)	0.123	
Hematuria n (%)	24 (100.0)	2 (6.7)	**0.001**	
CMV infection, n (%)	13 (54.2)	4 (13.3)	**0.003**	
CMV treatment response , n (%)	12 (92.3)	4 (13.3)	0.999	
CMV viral load (copy/ml), before treatment ,median (min-max)	5665 (481-1977826)	44852 (5487-104492)	0.412	
CMV viral load (copy/ml), after	97	130	0.549	

treatment, median (min-max)	(0-1869015)	(0-130)		
CMV treatment, n (%)				
Ganciclovir	5(20.8)	4 (13.3)	0.489	
Cidofovir	5 (20.8)	0 (0.0)	**0.013**	
Ganciclovir+ Cidofovir	3 (12.5)	0 (0.0)	0.082	
No treatment	11 (45.8)	26 (86.7)		
GVHD, n (%)	14 (58.3)	10 (33.3)	0.099	
Types of GVHD, n (%)				
Skin	10 (71.4)	3 (30.0)	0.098	
Intestinal	3 (21.4)	3 (30.0)		
Liver	1 (7.1)	4 (40.0)		
Days to neutrophil engraftment, median (min-max)	15 (9-30)	15 (9-28)	0.999	
Time of BKPyV-HC occurring after HSCT, month, median (min-max)	2 (1-15)	15 (7-59)	**0.001**	
Mortality, n (%)	9 (37.5)	4 (13.3)	0.056	
Immunosuppressive therapy, n (%)	19 (79.2)	17 (56.7)	0.145	
GVHD prophylactic regimen, n (%)				
Cyclophosphamide	0 (0.0)	1 (3.3)	0.999	
Corticosteroids	15 (62.5)	4 (13.3)	**0.001**	
Methotrexate	17 (70.8)	4 (13.3)	**0.001**	10.93 (2.6-45.7) **0.0**
MMF (Mycophenolate Mofethyl)	11 (45.8)	3 (10.0)	**0.004**	
Cyclosporine	19 (79.2)	11 (36.7)	**0.002**	
Tacrolimus	3 (12.5)	1 (3.3)	0.312	
Photophoresis	3 (12.5)	0 (0.0)	0.082	
CRE, pre-cidofovir, mean±sd	0.85 ±0.45	-		
GFR, pre-cidofovir, mean±sd	93.3 ±32.5	-		
CRE, post-cidofovir, mean±sd	0.97 ±0.44	-		
GFR, post-cidofovir, mean±sd	91.4 ±34.5	-		
Gross hematuria	20 (83.3)	0 (0.0)	**0.001**	
BK viremia, n (%)	5 (20.8)	0 (0.0)	**0.013**	
Nephrotoxicity, n (%)	1 (4.2)	-		
BK virus treatment, n (%)				
Cidofovir	18 (75.0)	-		
Ciprofloxacin	11 (45.8)			
Cidofovir use, n (%)				
Intravenous only	12 (50.0)			
Intravesical only	4 (16.7)	-		
Both	2 (8.3)			

CMV; Cytomegalovirus**, GVHD;** Graft versus host disease, **CRE;** Creatinine clearance**, GFR;** The glomerular filtration rate,

Table 2. Characteristics of BKPyV infection and Stem Cell Transplant patients with and without hemorrhagic cystitis

Characteristics	**with HC (n=19)**	**without HC (n=5)**	*p*
Urinary Viral load (copy/ml)	90000000 (21900-690000000)	938000 (1110-413000000)	0.103
Blood viral load (copy/ml)	126 (26-90000000)	76 (26-22800)	0.469
Treatment			
Quinolone antibiotics (ciprofloxacin)	10 (52.6)	1 (20.0)	0.327
Continuous bladder irrigation with water	0 (0.0)	3 (60.0)	**0.005**
Cidofovir treatment, n (%)	**17 (89.5)**	**1 (20.0)**	**0.006**
Intravenous only	12 (63.2)	0 (0.0)	**0.037**
Intravesical only	3 (15.8)	1 (20.0)	0.999
Both	2 (10.5)	0 (0.0)	0.999
Nephrotoxicity, n (%)	1 (5.3)	0 (0.0)	0.999
Outcome after initial therapy, **n (%)**			
Complete clinical response	10 (52.6)	3 (60.0)	0.999
No response	9 (47.4)	2 (40.0)	0.999