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Characteristics and Risk Factors for Patients with BK Polyomavirus Infection After Hematopoietic Stem Cell Transplantation

Hematopoetik Kök Hücre Nakli Sonrası BK Polyomavirüs İnfeksiyonu Gelişen Hastaların Klinik Özellikleri ve Risk Faktörleri

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ABSTRACT

Introduction: *BK polyomavirus (BKPyV) infections are an important cause of morbidity and mortality after hematopoietic stem cell transplantation (HSCT). The aim of the study was to assess the clinical characteristics of BKPyV infections after HSCT.*

Materials and Methods: *The study was conducted in the adult HSCT clinics of a tertiary hospital in the central of Turkey between January 2017 and December 2019.*

Results: *A total of 54 patients with HSCT were retrospectively evaluated and BKPyV disease was seen in 24 (44%). Hemorrhagic cystitis (HC) was seen in 19 (79.2%) of these patients. The median age was 42 and 50% of them were male. The most common underlying disease was acute myeloid leukemia. Five patients had autologous and 15 patients had allogeneic HSCT. The median time to engraftment was 15 days. Graft Versus Host disease (GVHD) was seen in seven patients. The median time elapsed to BKPyV disease after HSCT was found as 60 days. Nineteen patients with BKPyV disease had grade three and one patient had grade two HC. While BKPyV viremia was positive in five patients, viruria was detected in all patients. Eighteen of the patients with BKPyV disease were treated with cidofovir and 11 with ciprofloxacin. Four of the patients received intravesical cidofovir. The complete response was obtained in 53% of patients with BKPyV disease.*

Conclusion: *We found that coincidental BKPyV disease and CMV activation may occur after HSCT with haematological malignancies. It is thought that follow-up in patients with suspected activation, especially in terms of hematuria and cystitis, may be important. Also, immunosuppressive agents used for GVHD prophylaxis can trigger BKPyV disease.*

Key Words: *BK polyomavirus; Infection; Hematopoietic stem cell transplantation*

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ÖZ

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Giriş: *BK polyomavirus (BKPyV) infeksiyonları hematopoietik kök hücre transplantasyonu (HKHT) sonrası önemli bir morbidite ve mortalite nedenidir. Bu çalışmanın amacı, HKHT sonrası gelişen BKPyV infeksiyonlarının klinik özelliklerini ve risk faktörlerini değerlendirmektir.*

Materyal ve Metod: *Çalışma, Ocak 2017 ile Aralık 2019 tarihleri arasında Türkiye'nin merkezindeki üçüncü basamak bir hastanenin yetişkin HKHT kliniklerinde gerçekleştirilmiştir.*

Bulgular: *HKHT'li toplam 54 hasta geriye dönük olarak değerlendirildi ve 24'ünde (%44) BKPyV infeksiyonu görüldü. Bu hastaların 19'unda (%79.2) hemorajik sistit görüldü. Ortanca yaş 42 olup, bunların %50'si erkekti. Altta yatan en yaygın hastalık akut miyeloid lösemiydi. Beş hastada otolog, 15 hastada allojenik HKHT vardı. Engraftmana kadar geçen medyan süre 15 gündü. Yedi hastada Graft Versus Host hastalığı (GVHD) tespit edildi. HKHT sonrası BKPyV hastalığına kadar geçen medyan süre 60 gün olarak bulundu. BKPyV hastalığı olan 19 hastada üçüncü derece ve bir hastada ikinci derece hemorajik sistit vardı. Beş hastada BKPyV viremi görülürken, tüm hastalarda virüri tespit edildi. BKPyV hastalığı olan hastaların 18'i cidofovir ve 11'i siprofloksasin ile tedavi edilmişti. Hastaların dördü intravezikal sidofovir almıştı. BKPyV hastalığı olan hastaların ise %53'ünde tam yanıt alınmıştı.*

Sonuç: *Çalışma sonunda, hematolojik maligniteli hastalarda HKHT sonrası tesadüfi BKPyV hastalığı ve CMV aktivasyonunun ortaya çıkabileceği bulundu. Aktivasyon şüphesi olan hastalarda özellikle hematüri ve sistit açısından takibin önemli olabileceği düşünülmektedir. Ayrıca GVHD profilaksisi için kullanılan immünosupresif ajanlar da BKPyV hastalığını tetikleyebilir.*

Anahtar Kelimeler: *BK polyomavirüs; İnfeksiyon; Hematopoetik kök hücre nakli*

INTRODUCTION

BK virus, one of the known polyomavirus types, is an important cause of morbidity and mortality in patients with hematological malignancy after hematopoietic stem cell transplantation (HSCT). Firstly, it was isolated from urine specimens of renal transplant patients in 1970[1-3]. BK polyomavirus (BKPyV) associated infection is acquired in childhood and the virus becomes latent in the urothelial epithelial cells. The virus can usually be reactivated and cause urothelial mucosal damage, ureteral stenosis, nephropathy and hemorrhagic cystitis in immune compromised patients[1,4]. The infection usually occurs after HSCT as an asymptomatic virus or hemorrhagic cystitis (HC). Recent studies have reported that 5-68% of HC occurs after HSCT[5]. Several risk factors such as the use of immunosuppressive drugs, allogeneic transplantation, development of Graft Versus Host disease (GVHD), to be a carrier for BKPyV before transplantation may contribute to the development of HC[1]. While early-onset HC can be seen in the first week after HSCT, late-onset HC can be seen during 2nd week and six months after transplantation[1,6]. There is no standard treatment for BKPyV associated HC. Generally, reducing the dose of immunosuppressive drugs is recommended in the absence of GVHD. Cidofovir (intravesical or intravenous), ciprofloxacin and leflunomide are the drugs may be effective in the treatment of BKPyV infection after HSCT[6,7].

We aimed to evaluate the clinical characteristics of BKPyV infection in patients with haematological malignancies after HSCT. We also analyzed the risk factors for BK virus infection in this study group.

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 1 January 2017 to 30 December 2019. These units have 35 beds for patients undergoing HSCT.

This study included all hematological malignancy patients who underwent HSCT> 18 years old and subsequently developed BK viremia or viruri with urinary BK virus load >7 log10 copies/mL. Patients who did not have sufficient data or died before completing the follow-up period were not included in the study. In addition, patients who underwent HSCT but did not develop BKPyV disease included to the control group. There is no routine screening for BKPyV. The BKPyV analyses (urine or blood) were performed for patients with hematuria or urinary symptoms with no known previous etiology.

Data of demographic and clinical characteristics of patients were obtained from medical reports. These data included age, gender, primary malignancy, type of transplantation, the use of immunosuppressive drugs, development of GVHD, the number of the days elapsed to the engraftment, the presence of hematuria or HC, BKPyV-PCR level of urine and blood samples, the drugs used for the treatment of BK virus infection (also supportive treatments), the development of any cytomegalovirus (CMV) reactivation, the drugs used for the treatment of CMV infection.

The procedures routinely performed during allogeneic and autologous HSCT in our center:

Allogeneic SCT Prosedure

Acute myeloid leukemia (AML) patients are in the cytogenetically good/moderate-risk group, and these patients receive cytarabine (200 mg/m^2/day for 1-7th days), doxorubicin (25 mg/m^2/day for 1-3rd days) for remission-induction; high-dose cytarabine (2 x 3000 mg/m^2/day 1, 3, 5th days) chemotherapy is given for consolidation. Allogeneic SCT is performed from a fully matched individual with no previous donor.

Myeloablative regimen [cyclophosphamide (60 mg/kg/d on days -8th and -7th) and busulfan (3.2 mg/kg/d on days -5th to -2nd)] are used as a preparatory regimen in AML patients. Cyclophosphamide (2 x 300 mg/m^2/day 1-3rd days), doxorubicin (50 mg/m^2/day 4th day), vincristine (2 mg/day 1, 8, 15th days), L-asparaginase (20000 units/day 1, 8, 15th days) chemotherapies are applied to patients who are diagnosed Philadelphia (-) acute lymphoblastic leukemia (ALL). GVHD is a complication that occurs in the patient after HSCT from both related and unrelated donors. Patients are followed up for GVHD according to recommendations of the European Society for Blood and Marrow Transplantation (EBMT). In order to prevent GVHD in acute leukemia patients who underwent allogeneic SCT from a fully matched donor as a routine practice, CsA is started at 3 mg/kg IV -1 day and continued at 5 mg/kg/day orally when engraftment occurs. The dose is adjusted with the drug level and is continued until the +180th day. Methotrexate (MTX) is IV +1st (15 mg/m^2), +3rd (10 mg/m^2) and +6th (10 mg/m^2) is given routinely on days. Ursodeoxycholic acid (3 x 250 mg tb) is given to prevent liver GVHD[8,9]. Also, anti-infective prophylaxis included rifaksimin 2 x 200 mg/daily, valacyclovir 500 mg twice/daily, fluconazole 400 mg/daily, and trimethoprim/sulfomethoxazole (starting with 1 x 1 transplant protocol three days a week) for allogeneic SCT patients in accordance with institutional guidelines.

Autologous SCT Procedure

Cyclophosphamide (4 gr/m^2 on day +1st day) and G-CSF were used as mobilization regimens in patients with lymphoma. Carmustine (300 mg/m^2/day -7th day), etoposide (200 mg/m^2/day -6th and -5th days), cytarabine (200 mg/m^2/day -6th and -5th days) and melphalan (140 mg/m^2/day -1st day) were used. Autologous SCT is performed with melphalan (200 mg/m^2 -2nd day) following mobilization with cyclophosphamide (2.4 g/m^2 on day +1st day) and G-CSF (filgrastim 10 µg/kg/day), on 5th day. Anti-infective prophylaxis included levofloxacin 500 mg daily, valacyclovir 500 mg twice daily, and fluconazole 400 mg daily for autologous SCT patients. Routine approach for patients undergoing HSCT: All patients undergoing allogeneic SCT quinolone prophylaxis initiated, after transplantation until to neutrophil engraftment.

If hematuria is confirmed we firstly start hyperhydration. Also, If BKPyV disease is confirmed bladder irrigation or cidofovir (3-5 mg/kg/week IV or intravesical) are used. Probenecid is used concomitantly with cidofovir therapy to reduce nephrotoxicity[1].

Additionally, as the G-CSF, 10 µg/kg/day filgrastim (Neupogen®, Amgen Inc.), dose was divided into two and started subcutaneously to

be administered on day +5 and continued to be administered until sucient amount of CD34 (+) cells were collected. Approximately 2-3 weeks after the mobilization, all patients received conditioning with melphalan 200 mg/m^2 (reduced to 140 mg/m^2 in patients with renal insufficiency or >65 years old) on day -2, followed by infusion of autologous stem cells on day 0. These treatments are started 60 to 100 days after transplantation and discontinued six to nine months after transplantation without GVHD.

Definitions

BKPyV virus disease was defined as the detection of BKPyV by PCR testing in patients with genitourinary symptoms. The diagnostic triad of BKPyV-HC was defined according to European Conference on Infections in Leukaemia (ECIL) guideline; clinical symptoms of cystitis like abdominal pain and dysuria, grade two or higher haematuria, BK viral loads of urine is >7 log^{10} copies/mL or plasma viral loads of BKPyV can be 3-4 log^{10} copies/mL[1]. The severity of haematuria is described like grade one (microscopic haematuria), grade two (macroscopic haematuria), grade three (clots and macroscopic haematuria), grade four (grade three with renal failure to urinary obstruction)[1,10]. The cidofovir related nephrotoxicity is assessed by creatinine clearance estimated by the Cockcroft and Gault formula, before the first dose and after the last dose of cidofovir[6]. If the GFR value of the patient was normal before cidofovir treatment, there was an increase after, the use of a concomitant nephrotoxic agent was also questioned. If not, nephrotoxicity was associated with cidofovir use. Also, nephrotoxicity was defined as an increase in the serum creatinine concentration of at least grade two during the first course of cisplatin chemotherapy, as assessed on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

While neutrophil engraftment is defined as an absolute neutrophil count (ANC) >0.5 x 10^9/L for three consecutive days, platelet engraftment was defined as platelet count >20 x 10^9/L and then >50 x 10^9/L for three consecutive days without platelet support.

Complete clinical response is defined as improving the hematuria symptoms completely; partial response is the downgrading of hematuria. Clinical failure; as worsening hematuria or no changes in urinary symptoms[1,5].

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 9-50*107 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 them. The median age was 42 (range, 20 to 68), 50% were male. The most underlying disease of patients was AML (62%). Nineteen (79.2%) patients had allogeneic and five (20.8%) patients had autologous SCT. The patients were followed for approximately 12 months. The median interval between HSCT and the onset of BKPyV disease was two months (range, 1 to 15). The median time to neutrophil engraftment was 15 days (range, 9 to 30). Patient characteristics with or without BKPyV disease are presented in Table 1. GVHD was developed in fourteen of patients (71% skin, 21%

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) p
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 (%)	19 (79.2)	0	**0.001**	
Hematuria, Grade, n (%)				
Grade 1	4 (16.7)	2 (100.0)		
Grade 2	1 (4.2)	0 (0.0)	0.123	
Grade 3	19 (79.2)	0 (0.0)		
Grade 4	0 (0.0)	0 (0.0)		
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 treatment, median (min-max)	97 (0-1869015)	130 (0-130)	0.549	
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)	-	**0.001**	
Mortality, n (%)	9 (37.5)	4 (13.3)	0.056	
Immunosuppressive therapy, n (%)	19 (79.2)	17 (56.7)	0.145	

Table 1. Characteristics of stem cell transplant patients with and without BK polyomavirus (continue)

Characteristics	BK virus disease (n= 24)	Non BK virus disease (n= 30)	p	Multivariate analysis OR (95% CI) p
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**	
MMF (Mycophenolate Mofethyl)	11 (45.8)	3 (10.0)	**0.004**	**10.93**
Cyclosporine	19 (79.2)	11 (36.7)	**0.002**	**(2.6-45.7)**
Tacrolimus	3 (12.5)	1 (3.3)	0.312	**0.001**
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.

gastrointestinal and 7% liver respectively) and all diagnosed by histopathological examination. The most common GVHD prophylaxis administered for BK virus disease group was CsA (79%), MTX (71%), glucocorticoids (62%) followed by MMF (46%).

CMV infection was detected in 13 (54%) of patients with BKPyV disease and four (13%) of patients with non-BK virus disease. First, immunosuppressive therapy doses were reduced by half in all patients. Among the patients with BKPyV disease, five patients received ganciclovir intravenous IV (5 mg/kg/day bid), five patients received cidofovir IV (dose) and three patients received cidofovir (intravesical) plus ganciclovir (5 mg/kg/day bid) treatment. Treatment response was seen only in 12 patients, but no response was observed in one patient receiving cidofovir IV treatment.

HC was documented in 19 (79.2%) of patients after HSCT. Nineteen patients (79%) with BKPyV disease had grade-three, four patients (17%) had grade-one and only one patient (4%) had grade-two haematuria. The median time elapsed to BKPyV disease after HSCT was 60 days. While BK viremia was positive in five of 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 in patients with microscopic hematuria or the use of intravesical cidofovir. In patients with BKPyV disease, 9 (37%) patients have been treated with cidofovir, 3 (12%) patients with ciprofloxacin, 9 (37%) patients with ciprofloxacin plus cidofovir (5 mg/kg/day two times of the week).

Characteristics of BKPyV infection and SCT patients with and without hemorrhagic cystitis are

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

listed in Table 2. Twelve (50%) of them were treated with intravenous cidofovir, 4 (17%) patients with intravesical cidofovir. Two (8%) patients were treated with intravesical and intravenous combination cidofovir. Intravenous cidofovir was given 0.5-1 mg/kg 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. There was only one patient who developed renal function abnormalities or renal failure while receiving cidofovir therapy. After treatment of BKPyV-related HC, 10 (55%) patients achieved a complete response to the viruria or viremia and nine patients achieved no response. Probenecid has been administered oral preparation before therapy for patients treated with intravenous cidofovir. During the study period, 9 (37.5%) patients who developed BKPyV disease and 4 (13.3%) patients who did not develop disease died without any evidence of progression of the underlying disease.

Univariate analysis revealed that CMV reactivation and the previous 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, MTX, MMF, CsA was found the significant risk factor for BKPyV-related HC (hazard ratio 10.93, 95% CI 2.6-45.7, p= 0.001).

DISCUSSION

In recent years, BKPyV related HC cases have increasingly reported with the rise in allogeneic SCT and the widely use of immunosuppressive therapies in patients with haematological malignancies[1,2,5]. The overall incidence of BKPyV-HC is reported at 5-68%[1,2].

In recent studies, Hu et al. reported 21% BKPyV disease, 18% BK related HC among 38 HSCT recipients. Lunde et al. reported that in 1321 allogeneic transplant patients, HC developed 219 (17%) at a median of 22 days after alloHCT[11,12]. In another study of 102 allo-SCT patients, HC occurred in 25% and BKPyV was identified in 80% of patients[13]. In this current study, BKPyV was identified in 44% of 54 patients, HC occurred in 19 (79%) of patients with BKPyV infection. Although the small number of cases included, our incidence rates are seen as higher than reported in other studies. It is thought that these rates may be due to the high rates of stem cell transplantation applications and occurrence of GVHD in our centre due to the intensive immunosuppressive treatments.

The presence of GVHD and also the agents used for the treatment of the disease may be a risk factor for infections. Patients who develop acute GVHD are frequently treated with immunosuppressive drugs and high doses of systemic corticosteroids. Many previous studies have reported an association between BKPyV infection and immunosuppressive treatment. Immunosuppression resulting from GVHD itself and the effects of these medications cause an increased risk of HC by causing BKPyV replication and uroepithelial damage[1,10,14]. In the study conducted by Park Hoon et al. 18 of 69 allo-SCT patients had BKPyV related HC, and nine of them had acute GVHD previously. It was observed that only seven patients received antithymoglobulin therapy for in vivo T cell depletion. As a conclusion the study concluded that acute GVHD was found to be an independent risk factor associated with BKPyV infection[4]. However, in this current study, although GVHD was seen in 14 of patients (of all, 71% had skin, 21% gastrointestinal and 7% liver GVHD, respectively), there was no significant relationship with HC.

The most common agents used for GVHD prophylaxis (administered for BKPyV disease group) were CsA (79%), MTX (71%), glucocorticoid (62%) followed by MMF (46%). The use of immunosuppressive agents for GVHD prophylaxis was associated with high-risk factors of developing BKPyV-related HC in univariate analysis and in multivariate analysis, GVHD prophylaxis regimen was found significant risk factor. Therefore, according to the patients' BK virus risk status and GVHD grade, blood concentration level of immunosuppressive agent may be monitored and if necessary, dose modification should be considered[1,10].

Some studies have found an association between HC with CMV reactivation, suggesting that DNA viruses such as CMV can induce BKPyV replication in patients who underwent allogeneic SCT. They have demonstrated that reactivation of the BKPyV is very important in the development of HC after SCT. BKPyV could be detected in the urine after recovery as has been reported in the studies[15]. On the other hand, T cell depletion of bone marrow before transplantation was significantly associated with polyomavirus and CMV reactivation[16]. In our study, it was observed that CMV infections were more common in patients infected with the BKPyV and it was statistically significant. It is thought that CMV can induce BKPyV-related HC, and in this context, early initiation of treatment with ganciclovir may be beneficial to control CMV infection and reduce the occurrence of the HC.

Treatment options recommended for BKPyV related HC in are predominantly supportive therapies. Bladder irrigation, hydration can be used for the treatment of the urothelial damage. Cidofovir, ciprofloxacin and leflunomide have also demonstrated activity against BKPyV. 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[1,6]. Similarly with the previous reports, this current study favors cidofovir that it seems to be efficient for the management of BKPyV related HC despite its toxicity[1,6,17]. In our study, cidofovir treatment was initiated in 17 of 19 patients with HC, but nephrotoxicity was developed only in one and the clinical response rate was 52%, the mortality 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 BKPyV load[18,19]. 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 found statistically significant.

Whereas the recent recommendations include the reducing of immunosuppressive treatment as an essential management for BKPyV infection, it also carries a higher risk of rejection. Reducing the doses of immunosuppressive therapies to treat BKPyV infection is thought to carry a higher incidence of long-term chronic rejection[20].

CONCLUSION

We found, that BKPyV disease and CMV reactivation could occur incidentally after HSCT in patients with haematological malignancies. CMV infections may be a predictor of BKPyV infections. For this reason, it is thought that follow-up in patients with suspected CMV reactivation, especially in terms of hematuria and cystitis, may be important. In addition, GVHD was found to be a significant risk factor for BKPyV disease. It is thought that intense immunosuppressive agents used especially for GVHD prophylaxis may trigger BKPyV infection. Close monitoring of BK viremia or viruria in high-risk patients may be an important way to prevent HC. The mainstay of treatment may be to reduce the dose of immunosuppressive agents, with caution against the risk of rejection. However, due to the small number of cases reported in this study, large prospective randomized and well-controlled studies are needed.

ETHICS COMMITTEE APPROVAL

This study was approved by Erciyes University Clinical Research Ethics Committee (Decision no: 2020/34, Date: 15.01.2020).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: ZTY, AUK

Data Collection or Processing: MK, FC, AUK

Analysis/Interpretation: ZTY, AUK, MK, FC

Literature Search: MK, AUK, FC

Writing: ZTY, AUK

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