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BK virus incidence, risk factors and its effect on mortality in hematopoietic stem cell transplant patients-single center experience

 Mehmet Veysi Deviren¹,  Ahmet Sarici²,  Mehmet Ali Erkurt²,  Omer Faruk Bahcecioglu³,  Soykan Bicim²,
 İlhami Berber²,  Emin Kaya²,  Mustafa Ozgul²,  İrfan Kuku²

¹Cinar State Hospital, Department of Internal Medicine, Diyarbakir, Turkey²Inonu University, Faculty of Medicine, Department of Adult Hematology, Malatya, Turkey³Inonu University, Faculty of Pharmacy, Department of Clinical Pharmacy, Malatya, Turkey

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**Abstract**

The aim of this trial is to investigate the risk factors of BK viruria and the effect of BK viruria on mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). The data of 247 patients who underwent HSCT between 01.01.2011-01.12.2017 in Inonu University Faculty of Medicine Department of Hematology were retrospectively analyzed. BK viruria was defined as positive at any copy level in the urine. Of 247 patients, 97 patients (39.2%) were detected to have BK virus-positivity. Patients with positive BK virus in urine were younger than BK virus negative patients, and patients with multiple myeloma had a lower rate of BK virus positivity than other patients ($p<0.05$). The rate of BK viruria was found to be higher in patients who received busulfan and cyclophosphamide-containing conditioning regimens compared to patients who received other conditioning regimens (46% vs 28.9%, $p=0.007$). In addition, BK virus positivity was found to be lower in those receiving melphalan-based conditioning regimens than those receiving other conditioning regimens (28.6% vs 47.2%, $p=0.008$). BK virus positivity in urine was detected median 20 days after HSCT. BK virus positivity was detected in 80.4% (78/97) of the patients within the first 30 days. Patients with BK viruria had a higher first 100-day mortality than patients without BK viruria (17.5% vs 8%, $p=0.023$). In this series, BK viruria is a factor associated with mortality in the early period after HSCT and should be closely monitored in these patients.

Keywords: BK virus, hematopoietic stem cell transplantation, busulfan, cyclophosphamide, mortality

Introduction

Hematopoietic stem cell transplantation (HSCT) is performed for the treatment of many benign and malignant hematologic diseases every year. HSCT is divided into two groups as autologous and allogeneic, according to the donor [1]. Bacterial, viral, fungal and parasitic opportunistic infections are an important cause of mortality and morbidity following HSCT. The risk of opportunistic infection is determined by exposure to the pathogen, the immune system of the patient, and the virulence factors of the pathogen [2]. BK virus, one of these pathogens, was first reported in 1971. It was isolated from the uroepithelial cells of a renal transplantation patient diagnosed with urethral stricture. With the increasing use of immunosuppressive drugs, BK virus-dependent cases have

been reported, and there is evidence that it causes hemorrhagic cystitis (HC) in HSCT recipients since the 1980s [3]. Even though healthy individuals infected with the BK virus are asymptomatic, it remains latent in the renal tubule epithelial cells and can be reactivated in case of immunosuppression [4]. BK virus is related to many clinical conditions such as asymptomatic hematuria, hemorrhagic cystitis, urethral stenosis, developed in HSCT recipients. HC associated with BK virus usually occurs 3 to 6 weeks after HSCT [5]. In the previous trials, BK virus-associated hemorrhagic cystitis is an important cause of morbidity and mortality [6]. In case of serious immunosuppression, BK virus replication gets out of control and becomes symptomatic. It can be detected as asymptomatic in both allogeneic and autologous HSCT recipients, however, reactivation is more significant in allogeneic HSCT recipients [6].

It is aimed to investigate the effect of the BK viruria on mortality, hematuria and engraftment time. In addition, it was aimed to investigate risk factors for BK viruria.

*Corresponding Author: Mehmet Ali Erkurt, Inonu University, Turgut Ozal Medical Center, Department of Adult Hematology, Malatya, Turkey
E-mail: erkurtali@hotmail.com

Materials and Methods

The data of 247 patients who underwent HSCT between January 2011 and December 2017 in Inonu University Turgut Ozal Medical Center Hematology Department were retrospectively analyzed. It is approved by Inonu University Clinical Research Ethics Committee. (Approval number: 2018/ 23-9).

Data was obtained from the hospital electronic information system. Age, gender, disease group, transplantation type, pre-transplant conditioning regimen, BK virus positivity in the urine, presence of hematuria, neutrophil engraftment time and mortality in the first 100 days of our patients with BK virus (+) and (-) were compared.

BK viral load was measured by real time polymerase chain reaction method. BK viruria was defined as positive at any copy level in the urine.

Statistical analyses

IBM SPSS Statistics 22.0 program was used in the analyzes. Normality analysis of quantitative data was done with Shapiro Wilk test, comparison of qualitative data between two groups was done with Pearson chi-square test, and comparison of quantitative data between two groups was done with Mann-Whitney U test. Quantitative data are given as median and range. p values less than 0.05 were considered statistically significant.

Results

In the trial, of the 247 patients, 152 were male (61.5%) and 95 were female (38.5%). The age range of the patients is 18-77 years and the median age is 45 years.

BK virus was examined in 247 patients by considering that patients who underwent bone marrow transplantation between 2011 and

2017 in our HSCT center have complaints such as dysuria, polyuria and that there is microscopic and macroscopic hematuria in the urine. Of 247 patients, 97 patients (39.2%) were detected to have BK virus-positive. The demographic and clinical characteristics of 247 patients are given in table 1. We found that patients with positive BK virus in urine were younger than BK virus negative patients, and that patients with multiple myeloma had a lower rate of BK virus positivity than other patients ($p<0.05$).

The conditioning regimens administered to the patients before HSCT and BK virus positivity of patients is summarized in table 2. The rate of BK viruria was found to be higher in patients who received busulfan and cyclophosphamide-containing conditioning regimens compared to patients who received other conditioning regimens (46% vs 28.9%, $p=0.007$). In addition, BK virus positivity was found to be lower in those receiving melphalan-based conditioning regimens than those receiving other conditioning regimes (28.6% vs 47.2%, $p=0.008$).

BK virus positivity in urine was detected median 20 days after HSCT. BK virus positivity was detected in 80.4% (78/97) of the patients within the first 30 days.

The relationship between BK virus (+) in the urine and neutrophil engraftment time was analyzed and statistically significant difference was not found ($p=0.716$). While the median neutrophil engraftment time of BK virus (-) patients was 16 days, the median neutrophil engraftment time of BK virus (+) patients was detected as 16.5 days.

The first 100-day mortality of the 247 patients who underwent HSCT was analyzed. Seventeen of the 97 patients who were detected to have BK (+) in the urine died. A significant association was found between 100-day mortality and BK (+) (17.5% vs 8%, $p=0.023$).

Table 1. Demographic and clinical characteristics of our patients

	BK (+) patients (n=97)	BK (-) patients (n=150)	p value
Age, median (range)	42 (18-73)	48.5 (18-75)	0.004
Gender (Male:Female)	62:35	90:60	0.537
Diagnosis			
Multipl myeloma, n	15 (15.5%)	47 (31.3%)	0.005
Acute myeloid leukemia, n	35 (36.1%)	44 (29.3%)	0.267
Acute lymphoblastic leukemia, n	18 (18.6%)	19 (12.7%)	0.205
Hodgkin lymphoma, n	4 (4.1%)	8 (5.3%)	0.692
Non-Hodgkin lymphoma, n	19 (19.6%)	20 (13.3%)	0.165
Others, n	6 (6.1%)	12 (8%)	0.242
Transplantation type			
Allogeneic, n	47 (48.5%)	69 (46%)	0.168
Autologous, n	45 (46.4%)	79 (52.7%)	
Haploidentic, n	5 (5.1%)	2 (1.3%)	
Hematuria			
Present, n	47 (48.5%)	60 (40%)	0.19
Absent, n	50 (51.5%)	90 (60%)	

Table 2. The conditioning regimens of BK positive and BK negative patients

Conditioning regimens	BK positive patients (n=97)	BK negative patients (n=150)
Busulfan-Cyclophosphamide	45 (46.4%)	56 (37.3%)
Busulfan-Cyclophosphamide-Etoposide	24 (24.7%)	25 (16.7%)
High dose melphalan	15 (15.5%)	48 (32%)
Carmustine-Etoposide-Cytarabine-Melphalan (BEAM)	2 (2.1%)	4 (2.7%)
Busulfan-Fludarabine-Anti thymocyte globulin	4 (4.1%)	13 (8.7%)
Fludarabine-Cyclophosphamide-Anti thymocyte globulin	2 (2.1%)	1 (0.6%)
Fludarabine-Anti thymocyte globulin-Thiotepa-Melphalan	5 (5.1%)	3 (2%)

Discussion

HC is a well-known complication that occurs after HSCT. It reveals itself with a series of symptoms ranging from microscopic hematuria to severe bleeding which may cause obstructive nephropathy. HC occurs secondary to the use of conditioning regimens generally containing a high dose of cyclophosphamide in the early stage following HSCT. HC developed afterward generally occurs due to viruses, secondary to graft versus host disease (GVHD), or after the radiotherapy performed on the pelvic area. The most common viral pathogens which cause HC are adenoviruses, CMV, and BK virus [7]. BK viral load is determined by measuring the viral DNA amount in the urine and plasma using the PCR method. BK virus can be detected also in asymptomatic patients [8].

In the trial carried out by Dosin G and colleagues, HC was detected in 64 (15.7%) of 407 patients who underwent allogeneic HSCT, 56 (87.5%) of whom are proved to be caused by the virus. BK virus was detected in 48 patients, both BK virus and adenovirus in 5, both BK virus and CMV in 1 and adenovirus in 2 patients. In the univariate analysis, statistically, a significant difference was detected between HC and age ($p<0.001$, HLA matching ($p=0.04$), BK viral infection ($p<0.001$), CMV infection ($p=0.04$) and myeloablative conditioning regimen ($p=0.03$). In the multivariate analysis, HC was correlated with the BK virus ($p=0.0001$) and adenovirus ($p=0.0003$) infection. The 5-Year survival rate of the patients who underwent allogeneic SCT was 36%. Statistically, a significant difference was not detected between the patients having HC or not in terms of 5-year survival (25% and 39%, $p=0.20$) [7]. In our trial, a significant relationship was found between BK virus positivity and 100-day mortality.

In the trial carried out by Eksi et al. and published in 2018, the BK virus was examined in the serum and urine samples of 100 patients who underwent allogeneic HSCT. Upon the recommendation of the American Transplant Foundation, BK virus DNA copy number in urine $>10^7$, copy number in plasma $>10^4$ were considered as positive. In the urine trials of 100 patients who underwent allogeneic HSCT, while the BK virus was detected negative in 57 of them (57%), the BK virus was detected positive in 43 patients (43%). BK virus was detected positive within 50 days (range, 21-718) on average after HSCT. In patients who have BK virus copy number $>10^7$ /ml in the urine, conventional treatment (forced diuresis, bladder irrigation, hydration) was also provided together with levofloxacin (twice a day 500 mg po) treatment as

prophylaxis. Patients were responsive to the treatment and HC or significant HC (grade 4) did not develop. When serum samples of the same patients were analyzed, BK virus DNA was negative in the serum of 94 patients, while BK virus DNA copy number was detected as 44-319/ml in the serum of 6 patients and it was not clinically significant [9].

In the trial carried out by Lunde et al. and published in 2015, 1321 patients who underwent allogeneic HSCT were evaluated. Two hundred nineteen of 1321 patients (16.6%) developed HC. In patients who underwent allogeneic HSCT and developed HC, HC developed in 22 days on average. BK virus was inspected in the urine of 109 of 219 patients who developed HC [10].

In the trial carried out by Silva and colleagues, 209 patients were analyzed. HC was detected in 25 (11.9%) of 209 patients. BK virus was detected in the urine of 96 patients out of 209 patients who underwent allogeneic HSCT, and 15 of them (15.6%) developed HC. Also, BK was negative in the urine of 111 patients before HSCT, and 10 of them (9%) developed HC (HR 1.94, 95% CL, 0.9- 4.4; $p=0.095$). In the univariate analysis performed, HC was associated with conditioning regimen, intensity, and donor type in addition to the BK virus. The average hospitalization duration of the patients who developed HC within the first 100 days after HSCT was 41 days, and the hospitalization duration of the patients who did not develop HC was 26 days, and it was found statistically significant ($p=0.01$). Even though HC is important morbidity, the BK virus did not have an effect on survival [11]. In our trial, a significant relationship was found between BK viruria and 100-day mortality ($p=0.023$).

In the trial carried out by Rorije and colleagues, 491 patients were analyzed. 168 patients (34.2%) who underwent HSCT were examined in terms of the BK virus. Of 168 patients, 78 patients were detected to have BK virus-positive and 80 patients to have BK virus negative. Forty six of 78 patients developed HC (59%). When it is analyzed in terms of conditioning regimen content, BK virus was detected positive in the urine of 43 patients (55.1%) who use fludarabine, in 30 patients (38.5%) who use busulfan, in 43 patients (55.1%) who use cyclophosphamide, in 37 patients (47.4%) who use TBI, in 13 patients (16.7%) who use ATG, in 8 (10.3%) who use melphalan [12]. According to our trial, BK virus positivity in urine was found to be higher in patients who received the conditioning regimens involving busulfan and/or cyclophosphamide compared to those who received other regimens

in our trial ($p<0.05$). In addition, we found that BK virus positivity was lower in patients who were given melphalan than those who were not given melphalan ($p<0.05$).

In the trial carried out by Leung et al., 236 patients were analyzed. HC was detected in 32 (13.5%) patients and the patients did not have a history of urinary tract infection, pelvic radiotherapy, and kidney stone proved radiologically. In this study, a conditioning regimen involving busulfan and development of GVHD significantly increased the risk in patients who underwent allogeneic HSCT [13].

In a study investigating the risk factors of HC development after HSCT in patients with acute lymphoblastic leukemia, the risk of HC development in patients younger than 26 years was found to be 2.5 times higher than those above the age of 26 [14]. In another study of 90 patients who underwent allogeneic HSCT, BK viruria, myeloablative conditioning regimen and transplantation from unrelated donors were identified as risk factors for HC development [15]. In a prospective study of 59 patients who underwent allogeneic HSCT, cyclophosphamide-containing conditioning regimen, CMV reactivation and BK viremia were found to be risk factors for HC development [16].

In our trial, we found the conditioning regimen (busulfan and/or cyclophosphamide containing) and age as potential risk factors for BK viruria. We also found a lower incidence of BK viruria in patients receiving melphalan-containing conditioning regimen than in those receiving other conditioning regimens. Interestingly, we found a lower incidence of BK viruria in multiple myeloma patients compared to other patients. This may be related to the fact that patients with multiple myeloma are generally old and the use of melphalan in the pre-HSCT conditioning regimen.

The limitations of our study are the retrospective design of the study, the heterogeneity of the patients (both allogeneic and autologous transplant patients, having a wide variety of conditioning regimens), and the inability to evaluate the reasons that may cause BK virus reactivation, such as GVHD, because some data were not available.

Conclusion

In this trial, which is performed heterogeneous population but with a relatively large number of patients, it has been shown that BK viruria increases the first 100-day mortality in patients undergoing HSCT. Especially in patients with risk factors (eg. patients receiving busulfan and/or cyclophosphamide-containing conditioning regimen) BK viruria should be followed up strictly. Prospective trials are needed to determine risk factors in homogeneous populations with a large number of patients.

Conflict of interests

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Financial Disclosure

We have no financial disclosures for this article

Ethical approval

Ethics committee approval was obtained from Inonu University by the Ethics Committee for the study, ethics number 2018/ 23-9.)

References

1. Hatzimichael E, Tuthill M. Hematopoietic stem cell transplantation. *Stem Cells Cloning Adv Appl.* 2010;3:105-17.
2. Pranab Sharma Acharya SK. Infectious complications of hematopoietic stem cell transplantation. *J Stem Cell Res Ther.* 2013;s3:1-8.
3. Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. *Bone Marrow Transplant.* 2008;41:11-8.
4. Hirsch HH, Snyderman DR. BK Virus: Opportunity makes a pathogen. *Clin Infect Dis.* 2005;41:354-60.
5. Zaia J, Baden L, Boeckh MJ, et al. Viral disease prevention after hematopoietic cell transplantation. *Bone Marrow Transplant.* 2009;44:471-82.
6. Han SB, Cho B, Kang JH. BK virus-associated hemorrhagic cystitis after pediatric stem cell transplantation. *Korean J Pediatr.* 2014;57:514-9.
7. Dosin G, Aoun F, El Rassy E, et al. Viral-induced Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplant. *Clin Lymphoma Myeloma Leuk.* 2017;17:438-42.
8. Satyanarayana G, Marty FM, Tan CS. The polyomavirus puzzle: Is host immune response beneficial in controlling BK virus after adult hematopoietic cell transplantation?. *Transpl Infect Dis.* 2014;16:521-31.
9. Eksi F, Karsligil T, Gundes I, et al. Investigation of BK virus by real-time polymerase chain reaction in patients with allogeneic bone marrow transplantation. *Transplant Proc.* 2018;50:1510-3.
10. Lunde LE, Dasaraju S, Cao Q, et al. Hemorrhagic cystitis after allogeneic hematopoietic cell transplantation: risk factors, graft source, and survival. *Bone Marrow Transplant.* 2015;50:1432-7.
11. de Padua Silva L, Patah PA, Saliba RM, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplants is the complex result of BK virus infection, preparative regimen intensity and donor type. *Haematologica.* 2010;95:1183-90.
12. Rorije NMG, Shea MM, Satyanarayana G, et al. BK virus disease after allogeneic stem cell transplantation: A cohort analysis. *Biol Blood Marrow Transplant.* 2014;20:564-70.
13. Leung A, Mak R, Lie A, et al. Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. *Bone Marrow Transplant.* 2002;29:509-13.
14. El-Zimaity M, Saliba R, Chan K, et al. Hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: donor type matters. *Blood.* 2004;103:4674-80.
15. Giraud G, Bogdanovic G, Priftakis P, et al. The incidence of hemorrhagic cystitis and BK-viruria in allogeneic hematopoietic stem cell recipients according to intensity of the conditioning regimen. *Haematologica.* 2006;9:401-4.
16. Atilla E, Ates C, Uslu A, et al. Prospective analysis of hemorrhagic cystitis and BK viremia in allogeneic hematopoietic stem cell transplantation. *Turk J Haematol.* 2020;37:186-92.