BK VIRUS KAO UZROČNIK HEMORAGIČNOG CISTITISA KOD BOLESNIKA LEČENIH ALOGENOM TRANSPLANTACIJOM KOŠTANE SRŽI

ORIGINALNI RAD

BK POLYOMAVIRUS AS THE CAUSE OF HEMORRHAGIC CYSTITIS IN PATIENTS TREATED WITH ALLOGENEIC STEM CELL TRANSPLANTATION

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SAŽETAK

Uvod: BK virus je virus sa dvostrukim DNK lancem iz porodice *Polyomaviridae*. Na osnovu DNK sekvenci, može se klasifikovati u šest genotipova. Kod pacijenata uključenih u program alogene transplantacije matičnih ćelija hematopoeze (alo-TMĆH), dovodi do hemoragičnog cistitisa.

Cilj: Cilj ovog istraživanja je određivanje učestalosti *PCR (polymerase chain reaction)* pozitivnosti na BK virus u krvi i urinu bolesnika uključenih u program alo-TMĆH, određivanje prediktora za razvoj kliničke slike hemoragičnog cistitisa izazvanog BK virusom, kao i utvrđivanje njegovog uticaja na ukupno preživljavanja *(overall survival – OS)* bolesnika.

Materijali i metode: U retrospektivnu kohortnu studiju su uključena 42 bolesnika sa Klinike za hematologiju UKCS-a. Prisustvo virusa u krvi i urinu određivano je *PCR* metodom. Preživljavanje bolesnika u odnosu na pojavu hemoragičnog cistitisa računato je Kaplan-Majerovom metodom a poređenje je vršeno *log-rank* testom.

Rezultati: Pozitivan *PCR* nalaz na BK virus je bio prisutan u krvi kod 97,6% ispitanika, a u urinu kod 100% pacijenata. Prosečno vreme preživljavanja pacijenata bez kliničke slike hemoragičnog cistitisa je iznosilo 44,357 meseci, dok je za pacijente sa kliničkom slikom hemoragičnog cistitisa iznosilo 17,395 meseci. Na osnovu *log-rank* testa, uočena je statistički značajna razlika u preživljavanju između ovih grupa pacijenata ($p = 0,049$). Posmatrano u odnosu na dan engraftmenta leukocita, bolesnici sa engraftmentom nakon D+14 od dana alogene TMĆH, imali su značajno veću učestalost ispoljavanja kliničke slike hemoragičnog cistitisa ($p = 0,037$).

Zaključak: Hemoragični cistitis izazvan BK virusom predstavlja čestu komplikaciju u toku lečenja bolesnika sa malignim hematološkim oboljenjima u programima alogene transplantacije i značajno utiče na *OS* ovih bolesnika.

Ključne reči: alogena TMĆH, BK virus, hemoragični cistitis

ABSTRACT

Introduction: BK polyomavirus is a double-stranded DNA virus from the *Polyomaviridae* family. According to DNA sequences, this virus can be classified into six genotypes. In hematological patients enrolled in allogeneic hematopoietic stem cell transplantation (HSCT) programs, it can lead to hemorrhagic cystitis.

Aim: The aim of this study is calculating the prevalence of BK polyomavirus PCR (polymerase chain reaction) positivity in the blood and urine of patients involved in allogeneic HSCT, determining the predictive factors for clinical presentation of BK polyomavirus-associated hemorrhagic cystitis, as well as determining its effects on overall survival (OS) of the patients.

Materials and methods: This retrospective cohort study enrolled 42 patients from the Clinic of Hematology of the University Clinical Center of Serbia. The presence of the virus in blood and urine was determined by the PCR method. The survival rate of the patients in relation to hemorrhagic cystitis was calculated with the Kaplan-Meier method and comparison was performed with the log-rank test.

Results: A positive PCR result in the blood was found in 97.6% of the subjects, while urine tested positive in 100% of patients. The estimated survival time in patients without hemorrhagic cystitis was 44.357 months, while the group with the clinical presentation of hemorrhagic cystitis had an estimated survival time of 17.395 months. Based on the log-rank test, we found a significant difference in survival between those groups of patients ($p = 0.049$). With regards to leukocyte engraftment day, patients engrafted after D+14, had a higher frequency of hemorrhagic cystitis ($p = 0.037$).

Conclusion: BK polyomavirus-associated hemorrhagic cystitis is a common complication of treatment in patients suffering from hematological malignancies who are enrolled in an alo-HSCT program, and has a significant impact on OS..

Key words: allogenic HSCT, BK polyomavirus, hemorrhagic cystitis

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UVOD

BK virus je virus sa dvostrukim DNK lancem iz porodice *Polyomaviridae*. Na osnovu DNK sekvenci, virus se može klasifikovati u šest genotipova. Najčešći je tip I (80%), a sledi ga tip IV (15%) [1]. Virus je ubikvitaran i smatra se da do primoinfekcije, kod do 90% populacije, dolazi u predškolskom periodu. Nakon primoinfekcije, virus ostaje latentan u ćelijama bubrežnih tubula i epitelu mokraćne bešike, gde se može reaktivirati u stanjima imunosupresije, dovesti do viremije, te dati različite kliničke slike. Muški rod, starost i visoke doze imunosupresivne terapije su najznačajniji faktori rizika za reaktivaciju virusa.

Tokom reaktivacije, najčešće su zahvaćeni bubrezi – dolazi do nefropatije kod pacijenata sa transplantiranim bubregom [2], a zatim bešika sa kliničkom slikom hemoragičnog cistitisa, kod pacijenata u programu alogene transplantacije koštane srži. Postoje zabeleženi slučajevi infekcije nakon transplantacije srca, jetre i pluća [3,4,5], kao i jedna zabeležena BK virusna infekcija sa multiorganskom disfunkcijom kod deteta sa presađenim srcem [6].

U svetu, incidencija razvoja hemoragičnog cistitisa nakon alogene transplantacije koštane srži (alo-TMĆH) kreće se između 13% i 40% [7,8], dok su rezultati svakodnevne kliničke prakse na Klinici za hematologiju Univerzitetskog kliničkog centra Srbije (UKCS) pokazali da je incidencija kod ispitivanih bolesnika veća.

Primarni cilj ovog istraživanja jeste da odredi pozitivnost, u krvi i urinu, kod bolesnika uključenih u program alogene TMĆH pomoću *PCR* (engl. *polymerase chain reaction*) metode. Sekundarni cilj je određivanje incidencije prediktornih faktora za razvoj kliničke slike hemoragičnog cistitisa izazvanog BK virusom, kao i utvrđivanje njegovog uticaja na ukupno preživljavanje (engl. *overall survival – OS*) bolesnika u programu alogene TMĆH.

MATERIJALI I METODE

U retrospektivnu kohortnu studiju uključena su 42 bolesnika sa Klinike za Hematologiju UKCS-a, od toga 21 muškog i 21 ženskog pola, sa medijanom starosti od 38 godina, u opsegu od 19 do 57 godina. Bolesnici su imali dijagnoze Hočkinovog limfoma (HL), Nehočkinovog limfoma (NHL), akutne limfoblastne leukemije (ALL), akutne mijeloblastne leukemije (AML) i mijelodisplastičnog/mijeloproliferativnog sindroma (MDS/MPN).

Mikrobiološke metode

Reaktivacija BK virusa određivana je iz uzoraka krvi i urina *PCR* metodom. U analizu su bili uključeni samo pozitivni rezultati, do stotog dana od dana sprovođe-

INTRODUCTION

BK polyomavirus is a double-stranded DNA virus from the *Polyomaviridae* family. Based on the DNA sequences, the virus can be classified into six genotypes. The most frequent genotype is type I (80%), followed by type IV (15%) [1]. The virus is ubiquitous, and it is believed that, in 90% of the population, primo-infection occurs in the preschool period. After primo-infection, the virus remains latent in the renal tubule cells and in the epithelium of the urinary bladder, where it can become reactivated when the body is in a state of immunosuppression, causing viremia and producing different forms of clinical presentation. The male sex, age, and high doses of immunosuppressive therapy are the most significant risk factors for the reactivation of this virus.

During reactivation, kidneys are the organs most commonly affected – nephropathy develops in patients with a kidney transplant [2], followed by the urinary bladder, with clinical presentation of hemorrhagic cystitis in patients enrolled in the program of allogeneic bone marrow transplantation. There have been cases of infection recorded, following heart, liver, and lung transplantation [3,4,5], as well as a case of BK viral infection with multiorgan dysfunction in a child with a transplanted heart [6].

In the world, the incidence of the development of hemorrhagic cystitis following allogeneic bone marrow transplantation (allogeneic hematopoietic stem cell transplantation – allo-HSCT) is between 13% and 40% [7,8], while the results of everyday clinical practice at the Clinic for Hematology of the University Clinical Center of Serbia (UCCS) have shown a higher incidence in the tested patients.

The primary goal of this study is determining positivity in the blood and urine of patients involved in allogeneic HSCT, by means of the PCR (polymerase chain reaction) test. The secondary goal is determining the incidence of the predictors for the development of the clinical presentation of BK polyomavirus-associated hemorrhagic cystitis (BK-PyVHC), as well as determining its effects on overall survival (OS) of the patients enrolled in the program of allogeneic HSCT.

MATERIALS AND METHODS

The retrospective cohort study included 42 patients of the Clinic for Hematology of the UCCS, of whom 21 were male and 21 female patients, with the median age of 38 years, ranging from 19 to 57 years. The patients were diagnosed with Hodgkin lymphoma (HL), Non-Hodgkin Lymphoma (NHL), acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), or myelodysplastic/myeloproliferative syndrome (MDS/MPN).

nja procedure alogene TMĆH (D+100); *PCR* je rađen na 7 dana. Svim bolesnicima je, do D+100, jednom nedeljno određivan *PCR* status na BK virus u krvi i urinu. Za dan engraftmenta uziman je dan u kome je broj neutrofila bio iznad $1x10^9$ i broj trombocita iznad $20x10^{12}$. Dijagnoza hemoragičnog cistitisa je postavljana na osnovu mikrobioloških nalaza i postojanja hematurije.

Profilaksa i lečenje

Pojava hemoragičnog cistitisa prevenira se davanjem polispecifičnih imunoglobulina prvog, trećeg, sedmog, četrnaestog, dvadeset prvog, dvadeset osmog, pedeset šestog, sedamdeset četvrtog i osamdeset četvrtog dana od početka transplantacije.

Lečenje hemoragičnog cistitisa vrši se hidratacijom (3 l/m^2) alkalizacijom urina, primenom uroprotektora (mesna), kao i hinolonskim antibioticima. Klinički najteže forme leče se irigacijom mokraćne bešike rastvorom manitola i sorbitola. Od 2019. godine, za lečenje se koristi i antivirotik – cidofovir, koji prethodno nije bio dostupan.

Pre sprovođenja procedure alogene TMĆH, bolesnici prolaze kroz kondicione režime. Kondicioni režimi predstavljaju primenu hemioterapijskih agenasa i/ili zračne terapije pre alogene TMĆH, a po svojoj jačini se mogu podeliti na sledeće: mijeloablativno kondicioniranje (engl. *myeloablative conditioning – MAC*), koje dovodi do potpunog opustošenja koštane srži, i kondicioniranje smanjenog intenziteta (engl. *reduced-intensity conditioning – RIC*), koje koristi manje doze zračenja i ne dovodi do opustošenja koštane srži bolesnika.

Statistička obrada

Inicijalno je formirana baza podataka, grupisanjem i tabeliranjem rezultata po ispitivanim obeležjima bolesnika.

Deskriptivni statistički parametri izraženi su kroz medijanu i modus.

Četrnaesti dan nakon transplantacije matičnih ćelija označen je sa D+14.

Ukupno preživljavanje bolesnika obuhvatalo je period od momenta dijagnoze do smrtnog ishoda ili zaključno sa 2019. godinom, kod živih bolesnika.

Preživljavanje bolesnika u odnosu na lečenje analizirano je Kaplan-Majerovom metodom i upoređivano *log-rank* metodom.

Za statističku obradu podataka korišćen je softver *SPSS 23.0* za *Microsoft Windows*.

REZULTATI

Studijom su obuhvaćena 42 bolesnika – 21 muškarac (50%) i 21 žena (50%). Starost se kretala u rasponu od 19 do 57 godina, sa medijanom od 38 godina. Godine

Microbiological methods

Reactivation of the BK polyomavirus was determined from blood and urine samples with the PCR method. The analysis included only positive results registered until the 100th day following the allogeneic HSTC procedure (D+100); the PCR test was performed every 7 days. In all patients, the PCR status regarding the BK polyomavirus in the blood and urine was determined once a week, until D+100. The day when the neutrophil count was above $1x10^9$ and the platelet count was above $20x10^{12}$ was taken to be the day of engraftment. The diagnosis of hemorrhagic cystitis was established on the basis of microbiological findings and the presence of hematuria.

Prophylaxis and treatment

The development of hemorrhagic cystitis is prevented by administering polyspecific immunoglobulins, on days one, three, seven, fourteen, twenty-one, twenty-eight, fifty-six, seventy-four, and eighty-four after the beginning of transplantation.

Treatment of hemorrhagic cystitis is performed by hydration (3L/m^2), urine alkalization, the application of uroprotectors (mesna), as well as with the application of quinolone antibiotics. The clinically most severe forms are treated by irrigating the urinary bladder with a solution of mannitol and sorbitol. As of 2019, the antiviral drug – cidofovir, which had previously been unavailable, has been used for treatment.

Prior to the allo-HSCT procedure, patients undergo conditioning regimens. Conditioning regimens involve the application of chemotherapeutic agents and/or radiation therapy prior to allogeneic HSCT, and, depending on their strength, they can be categorized as: myeloablative conditioning (MAC), which results in complete ablation of bone marrow, and reduced-intensity conditioning (RIC), which uses smaller doses of radiation and does not lead to the ablation of the patient's bone marrow.

Statistical processing

Initially, a database was compiled by grouping and categorizing results in tables, according to the analyzed patient characteristics.

Descriptive statistical parameters have been expressed as the median and mode.

The fourteenth day following stem cell transplantation was designated D+14.

Overall patient survival covered the period from the moment of diagnosis until the lethal outcome, or concluding with the year 2019, in living patients.

Patient survival in relation to treatment was analyzed with the Kaplan-Meier method and was compared with the log-rank method.

Tabela 1. Demografske karakteristike

Table 1. Demographic characteristics

	Broj (%) / *Number (%)*
Medijana starosti / *Median age*	38
Opseg / *Range*	19 – 57
Muški pol / *Male sex*	21 (50%)
Ženski pol / *Female sex*	21 (50%)

Tabela 2. Učestalost dijagnoza

Table 2. Frequency of diagnoses

	Broj (%) / *Number (%)*
HL	8 (19%)
NHL	2 (4.8%)
AML	15 (35.7%)
MDS/MPN	2 (4.8%)
HLL	1 (2.4%)

starosti pri dijagnozi kretale su se u rasponu od 14 do 56 godina, sa medijanom od 34 godine (Tabela 1). Učestalost dijagnoza bolesnika obuhvaćenih istraživanjem bila je sledeća: ALL (35,7%), AML (33,3%), HL (19,0%), NHL (4,8%), MDS/MPN (4,8%), hronična limfoblastna leukemija – HLL (2,4%), (Tabela 2). U periodu praćenja do D+100, svi ispitanici (100%) su imali pozitivan *PCR* nalaz na BK virus u urinu, a 97,6% je imalo pozitivne *PCR* analize iz uzorka krvi. Kliničku sliku je razvilo 18 (42,9%) bolesnika, od kojih je sliku teškog hemoragičnog cistitisa imalo 13 (72,3%) pacijenata.

Do engraftmenta leukocita nije došlo kod tri bolesnika, pa je, od ukupno 39 bolesnika, kod njih 14 (35,9%) došlo do engraftmenta do D+14, dok je kod 25 (64,1%) pacijenata došlo do engraftmenta nakon više od D+14. Do engraftmenta trombocita nije došlo kod 7 bolesnika, a od ukupno 35 pacijenata, do engraftmenta do D+14 je došlo kod 4 (11,4%) bolesnika, a posle D+14 kod 31 (88,6%) pacijenta (Tabela 3).

Kod 30 (71,4%) bolesnika je primenjivan *MAC* režim, dok je preostalih 12 (28,6%) pacijenata bilo na *RIC* režimu.

The SPSS 23.0 for Microsoft Windows software was used for statistical data processing.

RESULTS

The study included 42 patients – 21 men (50%) and 21 women (50%). The patient age ranged from 19 to 57 years, with the median age being 38 years. The age at diagnosis ranged from 14 to 56 years, with the median age being 34 years (Table 1). The frequency of diagnoses in patients included in the study were as follows: ALL (35.7%), AML (33.3%), HL (19.0%), NHL (4.8%), MDS/MPN (4.8%), chronic lymphoblastic leukemia – CLL (2.4%), (Table 2). In the follow-up period until D+100, all of the subjects (100%) had a positive BK polyomavirus PCR test result in the urine, while 97.6% of them had a positive PCR test result in the blood. A total of 18 (42.9%) patients developed a clinical presentation, of whom 13 (72.3%) patients developed a severe clinical presentation of hemorrhagic cystitis.

Leukocyte engraftment did not occur in three patients, therefore, out of a total of 39 patients, in 14 (35.9%) patients engraftment occurred by D+14, while

Tabela 3. Kliničke karakteristike

Table 3. Clinical characteristics

	Broj (%) / *Number (%)*
Godine starosti pri dijagnozi, medijana / *Median age at diagnosis*	34
Godine starosti pri dijagnozi, opseg / *Age at diagnosis, range*	14 – 56
Engraftment leukocita pre 14. dana / *Engraftment of leukocytes before day 14*	14 (35.9%)
Engraftment leukocita posle 14. dana / *Engraftment of leukocytes after day 14*	25 (64.1%)
Engraftment trombocita pre 14. dana / *Engraftment of thrombocytes before day 14*	4 (11.4%)
Engraftment trombocita posle 14. dana / *Engraftment of thrombocytes after day 14*	31 (88.6%)
Postojanje hemoragičnog cistitisa / *Presence of hemorrhagic cystitis*	18 (42.9%)
Odsustvo hemoragičnog cistitisa / *Absence of hemorrhagic cystitis*	24 (72.3%)
Pozitivan *PCR* test urina / *Positive PCR urine test*	42 (100%)
Negativan *PCR* test urina / *Negative PCR urine test*	0 (0%)
Pozitivan *PCR* test krv / *Positive PCR blood test*	41 (97.6%)
Negativan *PCR* test krvi / *Negative PCR blood test*	1 (2.4%)

Tabela 4. Učestalost kondicionih režima prilikom alogene TMĆH

Table 4. Frequency of conditioning regimens applied in allogenic HSCT

	Broj (%) / *Number (%)*
HL	8 (19%)
NHL	2 (4.8%)
AML	15 (35.7%)
MDS/MPN	2 (4.8%)
HLL	1 (2.4%)

Učestalost primenjivanih kondicionih pretransplantacijskih režima bila je: *Flamsa-Bu* – kod 18 (42,9%) slučajeva, *FluBU2* – kod 9 (21,4%) slučajeva, *TBF-PostCy* – kod 8 (19,0%) pacijenata, *BuCy* – kod 4 (9,5%) bolesnika, *Threo Flu* – kod 3 (7,1%) slučaja (Tabela 4).

Na osnovu Kaplan-Majerove krive preživljavanja, prosečno vreme preživljavanja pacijenata bez kliničke slike hemoragičnog cistitisa iznosilo je 44,357 meseci (*CI* 95% = 43,3 – 168,6), dok je za pacijente sa razvijenom kliničkom slikom iznosilo 17,395 meseci (CI 95% = 43,3 – 168,6). Na osnovu *log-rank* testa, uočena je statistički značajna razlika u preživljavanju kod ove dve grupe pacijenata ($p = 0,049$), (Grafikon 1).

U odnosu na dan engraftmenta leukocita (pre ili posle D+14), Fišerovim testom tačne verovatnoće nije uočena značajna statistička razlika u odnosu na *PCR* pozitivnost testa uzorka krvi ($p = 0,641$), dok je Pirsonov hi-kvadrat test pokazao značajnu povezanost sa učestalošću razvoja kliničke slike hemoragičnog cistitisa ($p = 0,037$).

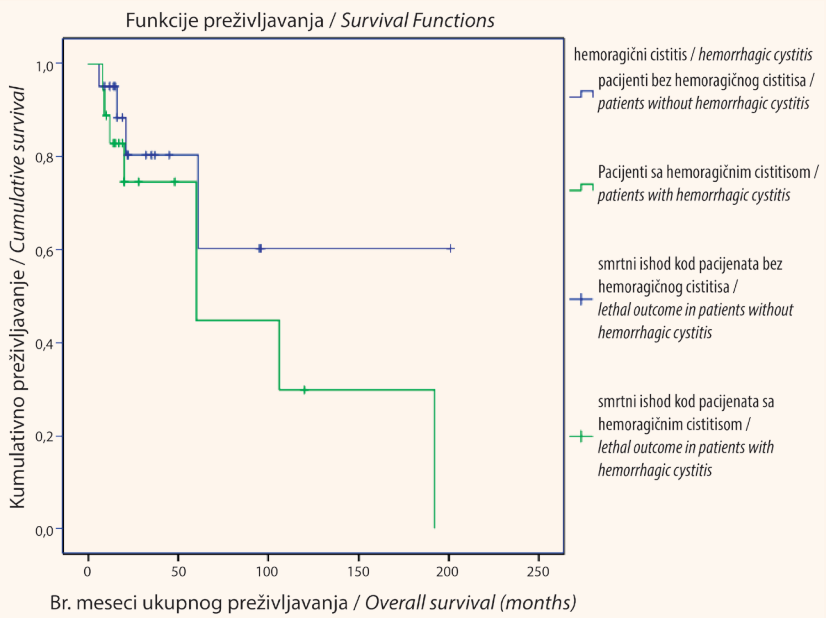
in 25 (64.1%) patients, engraftment occurred after D+14. Thrombocyte engraftment did not occur in 7 patients, and out of a total of 35 patients, in 4 (11.4%) patients, engraftment occurred by D+14, while in 31 (88.6%) patients, engraftment occurred after D+14 (Table 3).

In 30 (71.4%) patients, the MAC regimen was applied, while the remaining 12 (28.6%) patients were on the RIC regimen.

The frequency of the applied pre-transplant conditioning regimens was as follows: Flamsa-Bu – in 18 (42.9%) cases, FluBU2 – in 9 (21.4%) cases, TBF-PostCy – in 8 (19.0%) patients, BuCy – in 4 (9.5%) patients, Threo Flu – in 3 (7.1%) cases (Table 4).

Based on the Kaplan-Meier survival curve, the average survival time for patients without the clinical presentation of hemorrhagic cystitis was 44.357 months (CI 95% = 43.3 – 168.6), while it was 17.395 months (CI 95% = 43.3 – 168.6) for patients with a developed clinical presentation. Based on the log-rank test, a statistically significant difference in survival was found in these two groups of patients ($p = 0.049$), (Graph 1).

In relation to the leukocyte engraftment day (before or after D+14), the Fisher exact probability test did not establish a statistically significant difference in relation to the PCR test positivity of blood samples ($p = 0.641$), while the Pearson's chi-squared test showed a significant connection with the frequency of the development of the clinical presentation of hemorrhagic cystitis ($p = 0.037$).



* podaci za prva tri kvartala

Grafikon 1. Kaplan-Majerova kriva, koja prikazuje odnos očekivanog preživljavanja i postojanja hemoragičnog cistitisa

*data for the first three quarters

Figure 1. Kaplan-Meier curve showing different overall survival of patients with/without hemorrhagic cystitis

Fišerovim testom tačne verovatnoće, u odnosu na dan engraftmenta trombocita, nije pokazana značajna statistička razlika u odnosu na pozitivni *PCR* test uzorka krvi na BK virus (p = 0,886), kao ni u odnosu na razvoj kliničke slike hemoragičnog cistitisa (p = 1,000).

DISKUSIJA

Učestalost hemoragičnog cistitisa, kod pacijenata uključenih u program alogene TMĆH na Klinici za hematologiju UKCS-a, bila je veća od učestalosti objavljenih u dosadašnjoj literaturi [7,8,9]. Atila i saradnici su, u svojoj studiji, kao profilaksu koristili ciprofloksacin, a učestalost hemoragičnog cistitisa bila je 37%, što je manje u odnosu na naše rezultate [9]. Viremija, odnosno pozitivnost *PCR* testa iz uzorka krvi, bila je češća u našoj ustanovi u odnosu na studiju koju su sproveli Vu i saradnici, u kojoj se viremija javila u 67% transplantiranih slučajeva [10].

Virurija, odnosno pozitivnost *PCR* testa iz uzorka urina, bila je češća u našoj ustanovi, u odnosu na prospektivnu studiju koju su sproveli Laskin i saradnici, a koja je uključivala decu i mlade odrasle osobe. Rezultati njihove studije pokazuju pozitivnost u 45% slučajeva [11]. Ova dva podatka mogu govoriti u prilog većoj prokuženosti naše populacije BK virusom.

Naši rezultati Kaplan-Majerove krive preživljavanja podudaraju se sa rezultatima studije Kerbauja i saradnika, koja je uključivala 34 bolesnika u programu transplantacije koštane srži [12].

U dosadašnjoj literaturi nema podataka o povezanosti između dana engraftmenta trombocita i pojave kliničke slike hemoragičnog cistitisa, izazvanog BK virusom, što su pokazali i naši rezultati. Međutim, naše istraživanje je pokazalo da postoji značajna povezanost između dana engraftmenta leukocita i pojave kliničke slike hemoragičnog cistitisa izazvanog BK virusom (p = 0,037), ali u literaturi nismo pronašli objavljene rezultate slične našim.

Naša studija imala je nekoliko ograničenja. Posmatrana populacija bolesnika bila je heterogena, analiza je retrospektivna, a terapija hemoragičnog cistitisa se promenila u poslednjih godinu dana uvođenjem cidofovira, te je i ishod lečenja postao uspešniji, a samim tim je i ukupno preživljavanje postalo duže.

ZAKLJUČAK

Reaktivacija BK virusa i pojava viremije gotovo je neizbežna u populaciji naše ustanove, ali ovi parametri se nisu pokazali kao značajni prediktori. Velika učestalost *PCR* pozitivnosti na BK virus kod naših ispitanika sugeriše da bi bilo neophodno ispitati genetiku virusa i utvrditi da li postoje razlike u odnosu na druge populacije. Najznačajniji prediktor za razvoj kliničke slike

With the help of the Fisher exact probability test, relative to the thrombocyte engraftment day, significant statistical difference was not found in relation to a positive PCR blood test (p = 0.886), nor in relation to the development of clinical presentation of hemorrhagic cystitis (p = 1.000).

DISCUSSION

The incidence of hemorrhagic cystitis, in patients involved in the program of allogeneic HSCT at the Clinic for Hematology of the University Clinical Center of Serbia, was higher than the incidence reported in literature to date [7,8,9]. In their study, Atilla et al. used ciprofloxacin as prophylaxis, and the incidence of hemorrhagic cystitis was 37%. Which is lower when compared to our results [9]. Viremia, i.e., PCR positivity of blood samples, was more frequent in our hospital, as compared to the study carried out by Wu et al., where viremia occurred in 67% of the transplant cases [10].

Viruria, i.e., PCR positivity of the tests performed on urine samples, was more common in our hospital, as compared to the prospective study carried out by Laskin et al., which included children and young adults. The results of their study indicate positivity in 45% of the cases [11]. These two pieces of information may speak to a higher level of seroprevalence of the BK polyomavirus in our population.

Our Kaplan-Meier survival curve results coincide with the results of the study by Kerbauy et al., which included 34 patients enrolled in the program of bone marrow transplantation [12].

In literature published so far, there are no data on the connection between the day of thrombocyte engraftment and the occurrence of the clinical presentation of BK polyomavirus-associated hemorrhagic cystitis, which is also what our results have shown. However, our research has shown a significant connection between the day of leukocyte engraftment and the development of the clinical presentation of BK polyomavirus-associated hemorrhagic cystitis (p = 0.037), however, we did not find results similar to ours published in literature.

Our study had several limitations. The observed population of patients was heterogenous, the analysis was retrospective, whereas the therapy of hemorrhagic cystitis has changed in the past years with the introduction of cidofovir, whereby the treatment outcome has become more successful since then, consequently prolonging overall survival.

CONCLUSION

The reactivation of BK polyomavirus and the occurrence of viremia are practically inevitable in the population of our hospital, however, these parameters

hemoragičnog cistitisa je bio dan engraftmenta leukocita. Učestalost razvoja kliničke slike i njenih težih formi bila je veća ukoliko je vreme do engraftmenta bilo duže od 14 dana (>D+14).

BK hemoragični cistitis predstavlja čestu komplikaciju u toku lečenja bolesnika sa malignim hematološkim oboljenjima uključenih u program alogene transplantacije matičnih ćelija hematopoeze. On skraćuje prosečno preživljavanje i povećava troškove lečenja. Uvođenje profilakse adekvatnim antivirusnim agensom bilo bi potencijalno korisno u sprečavanju ove infekcije.

SPISAK SKRAĆENICA

TMĆH – transplantacija matičnih ćelija hematopoeze
UKCS – Univerzitetski klinički centar Srbije
PCR – lančana reakcija polimeraze (engl. *polymerase chain reaction*)
OS – ukupno preživljavanje (engl. *overall survival*)
HL – Hočkinov limfom
NHL – Nehočkinov limfom
ALL – akutna limfoblastna leukemija
AML – akutna mijeloblastna leukemija
MDS/MPN – mijelodisplastični/mijeloproliferativni sindrom
MAC – mijeloablativno kondicioniranje (engl. *myeloablative conditioning*)
RIC – kondicioniranje smanjenog intenziteta (engl. *reduced-intensity conditioning*)

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have not proven to be significant predictors. The high incidence of BK polyomavirus PCR positivity in our subjects suggests that it would be necessary to investigate the genetic makeup of the virus and determine whether there are differences, in comparison to other populations. The most significant predictor for the development of the clinical presentation of hemorrhagic cystitis was the day of leukocyte engraftment. The incidence of the development of the clinical presentation and its more severe forms increased if the time to engraftment exceeded 14 days (>D+14).

BK polyomavirus-associated hemorrhagic cystitis is a frequent complication in the treatment of patients suffering from malignant hematological diseases enrolled in the program of allogeneic hematopoietic stem cell transplantation. It shortens average survival and increases treatment costs. Introducing prophylaxis, in the form of an appropriate antiviral agent, would be potentially useful in the prevention of this infection.

LIST OF ACRONYMS AND ABBREVIATIONS

HSCT – hematopoietic stem cell transplantation
UCCS – University Clinical Center of Serbia
PCR – polymerase chain reaction
OS – overall survival
HL – Hodgkin lymphoma
NHL – Non-Hodgkin lymphoma
ALL – acute lymphoblastic leukemia
AML – acute myeloblastic leukemia
MDS/MPN – myelodysplastic/myeloproliferative syndrome
MAC – myeloablative conditioning
RIC – reduced-intensity conditioning

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