MAJOR ARTICLE

Cidofovir for BK Virus–Associated Hemorrhagic Cystitis: A Retrospective Study

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Background. BK virus–associated hemorrhagic cystitis (BKV-HC) is a severe complication after allogeneic hematopoietic stem cell transplantation (HSCT), but antiviral treatment for this condition has not been evaluated.

Methods. We conducted a retrospective survey on the safety and outcome of cidofovir treatment for patients with BKV-HC in centers affiliated with the European Group for Blood and Marrow Transplantation.

Results. From 1 April 2004 to 31 December 2007, 62 patients received a diagnosis of BKV-HC after a median interval of 35 days after HSCT (range, 3–577 days). Fifty-seven patients (92%) received intravenous cidofovir, whereas 5 patients received cidofovir intravesically. Complete response (CR) was recorded in 38 (67%) of 57 patients with HC treated with intravenous cidofovir, whereas partial response (PR) was documented in 7 patients (12%). CR was documented in 3 patients and PR in 1 patient with HC treated with intravesical cidofovir. A reduction of 1–3 logs in BKV load was documented in 8 of the 10 patients achieving CR. Mild-to-moderate toxic effects were recorded in 18 of 57 patients who received intravenous cidofovir administration. In a multivariate analysis, the factors significantly associated with response to cidofovir were the stem cell source ($P = .01$) and the use of total body irradiation ($P = .03$). After a median follow-up of 287 days, overall survival and total treatment-related mortality rates were 63% and 40% for patients achieving CR, compared with 14% and 72% for patients with PR or no response to cidofovir, respectively ($P < .001$ and $P = .001$, respectively).

Conclusions. Cidofovir may be a potentially effective therapy for BKV-HC, but evidence supporting its use requires randomized controlled trials.

Polyomavirus hominis type 1, called BK virus (BKV), has been associated with the occurrence of hemorrhagic cystitis (HC) in patients undergoing hematopoietic stem cell transplantation (HSCT) [1–6]. In most cases, BKV-HC occurs in the early postengraftment period, and it more frequently affects patients undergoing allogeneic than autologous HSCT. Accordingly, the alloimmune reaction of acute graft-versus-host disease (GVHD), or its treatment, may play a key role in the pathogenesis of BKV-HC [7–11].

Supportive measures have been the standard of care for many years, but new insights into the pathogenesis of late-onset HC have initiated the demand for a specific treatment inhibiting BKV replication [10–12]. Cidofovir is an acyclic nucleoside analogue that in in vitro studies demonstrates a broad range of antiviral activity, including BKV [13–15]. This drug is licensed for the treatment of cytomegalovirus retinitis in patients with AIDS and for ganciclovir-resistant cytomegalovirus infections, but encouraging case series may suggest its use

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for BKV-associated nephropathy in renal transplant recipients [16, 17]. Given its potential for nephrotoxicity, limited series at single institutions have been reported on the treatment of BKV-HC, so the paucity of data has left the indications for its use in HSCT recipients unresolved [6, 18, 19]. We report the results of a retrospective study on the safety and efficacy of cidofovir in the treatment of BKV-HC after allogeneic HSCT.

MATERIALS AND METHODS

The study was approved by the Scientific Committee of the European Group for Blood and Marrow Transplantation–Infectious Disease Working Party (EBMT-IDWP) and was presented at the IDWP session of the annual EBMT congress in Lyon, France, in 2007. A call for participation was subsequently sent to all centers by the EBMT central office. Data collection and processing were in accordance with standards at every center for patient confidentiality and good clinical practice. Transplantation protocols were approved by the local institutional review board, and all parents or patients gave their informed consent before HSCT.

Patient recruitment. Patients were eligible for the study if they had received cidofovir treatment for BKV-HC diagnosed after an allogeneic HSCT. BKV-HC was classified with regard to the variable degree of macroscopic hematuria, according to the grading score proposed by Droller et al. [20] and others: grade II, macroscopic hematuria; grade III, macroscopic hematuria with clots; and grade IV, macroscopic hematuria with renal or bladder dysfunction [6], with symptoms of cystitis and demonstration of concurrent BKV replication in urine or blood [3, 5, 6]. We excluded patients receiving cidofovir for HC not related to BKV infection or preemptive treatment for asymptomatic BK viruria and viremia with or without microscopic hematuria (i.e., grade I HC). Data on concurrent infective causes of cystitis were collected, but they did not represent a reason for exclusion from the study.

Patient management. All patients were treated in high-efficiency particulate–filtered air rooms during the neutropenic phase, and standard measures were adopted to prevent or treat toxic effects to the organ, GVHD, and infectious complications [21]. Hyperhydration, forced diuresis, and urine alkalinization were used in all patients during the conditioning regimen as preventive measures for drug-related chemical cystitis, whereas mercaptoethane sodium sulfonate was given to patients receiving cyclophosphamide.

Polymorphonuclear cell and platelet engraftment were defined as the first of 3 and 7 consecutive days on which polymorphonuclear cell and platelet counts exceeded 0.5×10^9 cells/L and 50×10^9 platelets/L, respectively. BKV replication in both urine and plasma was determined by polymerase chain reaction. The timing and frequency of testing were at the discretion of the treating physician.

Standard criteria were used to define transplantation-related mortality (TRM), infections, and acute or chronic GVHD [22–25]. Only the patients who had polymorphonuclear cell engraftment or survived at least 100 days after HSCT were considered assessable for acute and chronic GVHD, respectively.

The remission status of the underlying malignant disease was classified as controlled if the patient was in complete remission, partial remission, or chronic phase (only for patients with chronic myeloid leukemia) or had a diagnosis of refractory anemia; in the remaining patients, the underlying malignant disease was defined as uncontrolled. Complete response (CR) was defined as a complete resolution of HC after cidofovir treatment, whereas partial response (PR) was defined as a significant improvement of symptoms of HC but persistence of gross hematuria. Failure was considered as no improvement or worsening of HC.

Statistical analysis. The follow-up data were analyzed as of 31 December 2007. Where appropriate, patient characteristics were compared using χ^2 or Fisher's exact test for categorical variables [26]. TRM and overall survival (OS) were calculated from the date of HSCT to the date of any nonrelapse death or any death due to any cause, respectively, or to the date of latest follow-up. TRM was estimated by the cumulative incidence method, with death from relapse being the competing event [27]. OS was estimated by the Kaplan-Meier method. Host- or HSCT-related characteristics were assessed in the analysis of prognostic factors for efficacy of cidofovir therapy. Multivariate analysis was performed with SAS statistical software, version 9.1 (SAS Institute), and a logistic regression model; hazard ratios, 95% confidence intervals (CIs), and 2-sided P values were calculated [28]. The level of statistical significance was set at $\alpha = .05$.

RESULTS

From 1 April 2004 to 31 December 2007, 62 episodes of BKV-HC treated with cidofovir were recorded in 62 patients from 17 EBMT centers. Nine patients were recently described in a single case series [29, 30]. The median number of episodes was 3 per center (range, 1–12). In 2 episodes the administration of cidofovir was also indicated for concurrent adenovirus infection. There were 46 males (74%) and 16 females (26%), with a median age of 15.9 years (range, 2.5–62.3 years) at diagnosis of BKV-HC. The underlying medical diagnosis was acute leukemia in 36 patients (58%), chronic myeloid leukemia in 10 (16%), non-Hodgkin lymphoma in 5 (8%), other malignant diseases in 3 (5%), and nonmalignant disease in 8 (13%). In patients with malignant diseases, the remission status was defined as controlled in 45 (83%) and uncontrolled in 9 (17%). Thirty-three episodes (53%) occurred in patients younger than 18 years.

Characteristics of HC. HC was diagnosed at a median in-

Table 1. Summary of therapy with cidofovir.

Variable	Finding
Intravenous cidofovir	
Proportion (%) of treated patients	57/62 (92)
Median no. of doses (range)	4 (1–15)
First dose, median mg/kg (range)[a]	5 (0.5–5.7)
Patients experiencing toxic effects of cidofovir, proportion (%)	18/57 (32)
No. of patients experiencing toxic effects in the kidney	17
WHO toxicity score, no. (%) of patients	
I	4 (23)
II	7 (41)
III	3 (18)
IV	3 (18)
Myelotoxicity	1
Intravesical cidofovir	
Proportion (%) of patients treated	5 (8)
Median no. of treatments (range)	4 (1–5)
Median first dose, mg (range)	150 (50–200)
Toxicity of cidofovir	No

NOTE. WHO, World Health Organization.

[a] Thirteen patients received cidofovir, 0.5–1 mg/kg; and 44 patients received cidofovir, 3–5 mg/kg.

terval of 35 days (range, 3–577 days) after HSCT. Fifty-two (84%) of 62 episodes occurred after day 15, whereas 55 episodes (89%) were diagnosed by day 100 after HSCT. Severity of HC was scored as follows: grade II, 18 (29%); grade III, 34 (55%); and grade IV, 10 (16%). The median duration of HC was 30 days (range, 5–130 days).

The median hematologic parameters at diagnosis of HC were as follows: hemoglobin concentration, 9.9 g/dL (range, 6.9–14.8 g/dL); platelet count, 26.5×10^9 platelets/L (range, 6–300×10^9 platelets/L); and white blood cell counts, 2.6×10^9 cells/L (range, 0–15×10^9 cells/L). Testing for BK viruria was undertaken in 57 episodes, although the timing and frequency of testing were at the discretion of the investigator. In the remaining 5 episodes the search for BKV was performed only on blood ($n = 4$) or by cytologic testing ($n = 1$). Overall, the finding of BK viruria anticipated HC in 14 episodes (25%), coincided with the diagnosis of HC in 14 episodes (25%), and was first detected after the diagnosis of HC in 29 episodes (51%).

BK viremia was investigated in 39 episodes, and as for BK viruria, the timing and frequency of testing were determined at the discretion of the investigator. When tested, BK viremia preceded HC in 8 episodes (21%), coincided with HC in 4 episodes (10%), and was first detected after the diagnosis of HC in 27 episodes (69%). For the episodes of HC where BKV replication preceded the clinical diagnosis, the median time from first detection of BK viruria and BK viremia to development of HC was 22 days (range, 1–61 days) and 11 days (range, 1–35 days), respectively.

Treatment of HC. Table 1 summarizes the data regarding cidofovir therapy. Hyperhydration was used in 56 patients (90%), whereas bladder irrigation through a urethral catheter was added in 33 patients (53%). Blood and platelet transfusions were administered in 50 (81%) and 48 (77%) patients with HC, with a median number of transfusions of 6.5 (range, 1–210) and 12 (range, 1–276), respectively.

Fifty-seven patients (92%) received intravenous cidofovir, with a median number of doses given of 4 (range, 1–15). The starting dose of cidofovir was 0.5–1 mg/kg in 13 patients, whereas the remaining 44 patients received a dose of 3–5 mg/kg. Thirty-nine patients (68%) received probenecid as renal protection. Cidofovir-related toxic effects were recorded in 18 (32%) of 57 patients treated with intravenous cidofovir and were mainly related to the kidney. Moderate (grade I and II World Health Organization toxicity score) to severe (grade III and IV World Health Organization score) worsening of kidney function on the basis of the creatinine value was observed in 6 patients, but no patient required hemofiltration or hemodialysis after cidofovir administration. Only 1 patient had cytopenia related to cidofovir. Three patients died early of severe complications after HSCT (i.e., 2 patients died of severe acute GVHD and multiorgan failure on days 47 and 117, and 1 patient died of multiorgan failure on day 57). A fourth patient died of progression of the underlying disease at day 163.

Five patients (8%) received intravesical cidofovir at a median dose of 150 mg (range, 50–200 mg), with a median number of 4 doses (range, 1–5). One of these experienced bladder spasms during treatment that required antispasmodics and an-

	Weeks				
	1	2	4	6	8
CR					
No. of patients	22	17	19	13	6
Median log value	3.1	2.7	2.0	3.1	0
Range	0 - 6.2	0 - 5.4	0 - 5.4	0 - 6.1	0 - 6.6
PR/F					
No. of patients	7	7	4	5	1
Median	0	0	1.6	3.9	4.6
Range	0 - 5.4	0 - 5.1	0 - 4.1	0 – 4.8	

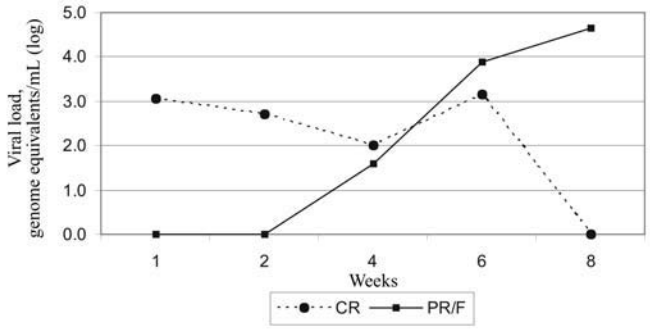

Figure 1. Modification of BK virus viremia over time expressed as log of viral load. The data correspond to the weeks of treatment with cidofovir. CR, complete response; PR/F, partial response/failure.

algesics. In the remaining patients, no organ toxic effects were reported.

Other potentially effective treatments for HC were used in 20 (32%) of 62 patients with HC as follows: hyperbaric oxygen therapy, 8 patients; leflunomide, 4 patients; intrabladder instillation of granulocyte-macrophage or granulocyte colony-stimulating factor, 3 patients; application of platelet gel by cystoscopy, 3 patients; and foscarnet, 2 patients; with 1 treatment each of ribavirin, lamivudine, ciprofloxacin, prostaglandin E, and estrogens.

Clinical and virologic response to cidofovir. A CR was recorded in 38 (67%) of 57 patients with HC treated with intravenous cidofovir, whereas a PR was documented in 7 patients (12%). No improvement or worsening was observed in 10 (18%) and 2 (3%) patients, respectively. Treatment with intravesical cidofovir was associated with CR in 3 patients, PR in 1 patient, and no improvement in the remaining patient. Overall, the response rate was not different in the 20 patients treated with cidofovir plus other potentially effective treatments: in this group, 11 were eventually classified as CR (55%) and 3 as PR (15%).

Among 41 patients with CR, 29 had detectable BK viremia, and 38 had BK viruria at HC diagnosis. Resolution of HC was associated with the complete clearance of BK viremia in 22 (81%) of 27 patients who had at least 1 follow-up test after starting cidofovir. The median time to BK viremia clearance was 37 days (range, 7–102 days).

BK viruria test results became negative in 6 (20%) of 30 patients who had at least 1 follow-up test after starting cidofovir therapy. In these patients, the median time to BK viruria clearance was 161 days (range, 16–357 days).

Figure 1 shows the modification of BKV load according to the type of clinical response and the time of BKV testing from the start of HC. A reduction of 1 log and 3 logs in the median value of BKV load was found in patients with a CR by 4 and 8 weeks after cidofovir treatment. The patients with PR or those in whom cidofovir therapy failed showed an increase of BK viremia by 4 weeks from the start of cidofovir administration.

Figure 2 shows the results of BK viremia in 10 patients who obtained CR and who had quantitative BKV estimations on blood samples before each cidofovir course. A reduction of $\geqslant$2 logs of BKV load was documented in 7 patients (5 permanent and 2 transient), whereas 3 patients did not have any modification of BKV load with cidofovir.

Risk factor analysis. Table 2 provides an analysis of factors associated with CR in patients treated with intravenous cido-

	Week					
Patient no.	1	2	4	6	8	Virologic response*
1	3.49	3.18	3.00			No
2	3.14	0.00	3.04	3.33		Yes, but transient
3	3.61	4.54	0.00			Yes
4	2.75	0.00	0.00	2.47		Yes, but transient
5	3.40	2.70		3.28	0.00	Yes
6	3.98	2.70	3.51	0.00		Yes
7	5.53	5.40	5.36	6.11	6.57	No
8	5.48	3.56				Yes
9	6.18	3.55				Yes
10	4.46	4.13	4.67	3.72		No

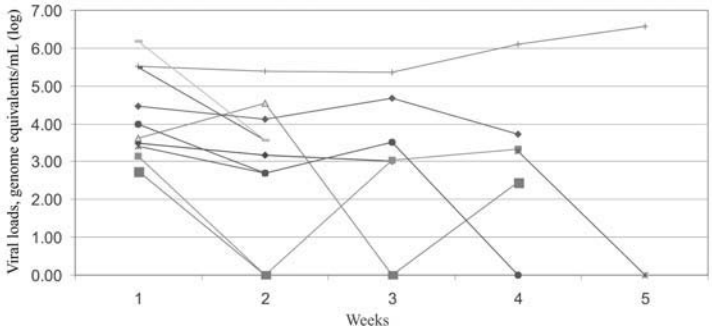

Figure 2. Modification of BK virus (BKV) viremia in 10 complete response (CR) patients who had BK viremia tested before every administration of cidofovir. *Decrease in BKV load of ⩾2 logs after cidofovir treatment.

fovir. In a univariate analysis, the following variables demonstrated significance: the source of stem cells ($P = .01$ for bone marrow or peripheral blood vs. cord blood), the use of total body irradiation ($P = .02$), and the earlier recovery of polymorphonuclear cells ($P = .045$). In multivariate analysis, the factors that remained significant were the stem cell source ($P = .01$; relative risk, 7; 95% CI, 2–32) and the use of total body irradiation ($P = .03$; relative risk, 7; 95% CI, 1–38).

TRM, OS, and event-free survival in patients with HC. After a median follow-up of 287 days (range, 52 days to 4.7 years), 29 patients were alive. The total TRM rate was 50% (95% CI, 35%–72%), whereas the 1-year OS rate was 39% (95% CI, 25%–53%). Twenty-six (63%) of 41 patients with CR were alive, compared with 3 (14%) of 21 patients with a PR or failure of response ($P < .001$). The total TRM rate for patients with CR after cidofovir treatment was 40% (95% CI, 21%–78%) versus 72% (95% CI, 54%–95%) for patients with a PR or failure of response ($P = .001$).

DISCUSSION

Although the pathogenesis of HC after allogeneic HSCT has not been completely elucidated, there is evidence that this complication is temporally correlated with engraftment, acute GHVD, and high-level urinary BKV replication [6, 10, 11]. Because of frequent excretion of BKV in the urine of healthy people and asymptomatic immunocompromised patients who have undergone chemotherapy or HSCT, high BKV load in urine (at least 3-log increase over baseline or a BKV load peak 10^8–10^9 copies/mL) has been suggested as a marker of late-onset postengraftment HC [2, 3, 8]. Recently, a BKV load 10^3–10^4 genomic copies/mL of blood has also been shown to be associated with late-onset postengraftment HC [5, 6].

These findings have generated interest in the use of a specific antiviral treatment for HC after HSCT in addition to the standard supportive measures used to date. Information on the use of cidofovir for BKV-HC in HSCT recipients mainly stems from case reports or case series [6, 17, 31]. Gorczynska et al. [18] and Savona et al. [19] reported a clinical response of 80% and 84%, respectively, in 2 case series of 19 children and 19 adults with resolution of BK viruria (by qualitative polymerase chain reaction) in 32% of patients or a decrease of at least 1 log of urinary BKV load in 47% of patients.

This article describes the largest series so far documenting the potential role of cidofovir in the treatment of BKV-HC after allogenic HSCT. In this series, male sex accounted for more than 74% of episodes, which is in accordance with previous reports [32, 33]. Most episodes occurred in the early posttransplantation period or just after the postengraftment phase, sup-

Table 2. Univariate and multivariate analysis of risk factors associated with response to treatment with intravenous cidofovir.

Patient characteristic	Proportion (%) of patients with CR to cidofovir	Univariate *P*	RR (95% CI)	Multivariate *P*
Sex				
Male	28/42 (67)		…	
Female	10/15 (67)	>.99	…	
Age at HSCT, compared with median age (15.8 years)				
Less than the median	24/31 (77)		…	
Greater than or equal to the median	14/26 (54)	.06	…	
Underlying disease				
Malignant	32/50 (64)		…	
Nonmalignant	6/7 (86)	.40	…	
Status of disease[a]				
Controlled	28/45 (62)		…	
Uncontrolled	4/5 (80)	.60	…	
HLA matching[b]				
Match	24/32 (75)		…	
Mismatch	11/21 (52)		…	
Haplotype	2/3 (67)	.20	…	
Stem cell source				
Bone marrow or peripheral blood	34/45 (76)		…	
Cord blood	4/12 (33)	.01	7 (2–32)	.01
Total body irradiation				
Yes[c]	16/18 (89)		…	
No[d]	22/39 (56)	.02	7 (1–38)	.03
Median TNC infused (bone marrow)[b]				
Less than the median	5/8 (63)		…	
Greater than or equal to the median	8/9 (89)	.30	…	
Median of ⩾34 CD cells infused (peripheral blood)				
Less than the median	10/12 (83)		…	
Greater than or equal to the median	9/14 (64)	.40	…	
Median TNCs infused (cord blood)[e]				
Less than the median	1/3 (33)		…	
Greater than or equal to the median	2/8 (25)	>.99	…	
Polymorphonuclear cell recovery,[f] compared with the median (17 days)				
Less than the median	18/22 (82)		…	
Greater than or equal to the median	19/34 (56)	.045	…	
Platelet recovery,[g] compared with the median (27 days)				
Less than the median	15/18 (83)		…	
Greater than or equal to the median	18/24 (75)	.70	…	

NOTE. CI, confidence interval; CR, complete response; HSCT, hematopoietic stem cell transplantation; RR, relative risk; TNC, total nucleated cells.

[a] Only malignant disease.

[b] Data missing for 1.

[c] Among these patients, 1 received a low dose of 2 Gy, 1 received a single dose of 9.9 Gy, and all the remaining patients received a fractioned dose of 12 Gy.

[d] Among these patients, 17 received a 3-drug regimen of the following drugs: busulfan, etoposide, fludarabine, melphalan, thiotepa, cyclophosphamide, treosulfan, cytarabine; 21 received a 2-drug regimen of the following drugs: busulfan, cyclophosphamide, melphalan, fludarabine, thiotepa, treosulfan, cytarabine, idarubicin, and one patient received a conditioning regimen with cyclophosphamide only. The median dose (range) of drugs was as follows: busulfan, 12.8 mg/kg (9.6–20 mg/kg); etoposide, 40 mg/kg (2 patients); fludarabine, 150 mg/m^2 (40–240 mg/m^2); melphalan, 140 mg/m^2 (120–140 mg/m^2); thiotepa, 10 mg/kg (8–15 mg/kg); cyclophosphamide, 120 mg/kg (40–200 mg/kg); treosulfan, 12 and 14 g/m^2 (2 patients); cytarabine, 500 and 9000 mg/m^2 (2 patients); and idarubicin, 24 mg/m^2 (1 patient).

[e] Data missing for 2.

[f] Data on 56 engrafted patients.

[g] Data on 42 engrafted patients (data not available for 3 patients).

porting the hypothesis that BKV-HC is a combination of 3 related phenomena (i.e., denudation of the urothelial transitional cell layer by conditioning [34], massive high-level BKV replication in the absence of virus-specific immune control, and the early posttransplantation immune reconstitution [1, 11]). Given the retrospective nature of this study, it is not possible to determine the value of BK viremia and BK viruria in predicting the development of clinically overt HC. In the subgroup of patients who were monitored prospectively, BK viruria preceded HC earlier than BK viremia, with a median of 22 versus 11 days. On the other hand, in our recent experience of 15 patients undergoing allogeneic HSCT who were monitored prospectively during the first 3 months after transplantation, BK viremia had a higher specificity and positive predictive value than BK viruria of 82% and 67% versus 64% and 50% [6].

CR was recorded in 66% of patients treated with cidofovir, whereas an additional 13% obtained a PR with a clinical improvement. These results are comparable to those reported by others in smaller series and support the view of a clinical benefit of cidofovir treatment for BKV-HC. Regarding the virologic response, the data clearly indicate that BK viremia may serve as an early marker of cidofovir treatment failure by showing significant increases in plasma BKV loads despite cidofovir treatment. By contrast, in patients with CR the BKV load remained low or even decreased over time. In the responding patients, BKV was cleared from blood in 81% of HC episodes versus 20% clearance of BKV from urine. The median time to BKV clearance was 37 days for blood versus 161 days for urine.

Despite these findings, this study did not allow us to demonstrate a definite role for cidofovir in curing BKV-related HC because of its retrospective, uncontrolled design and the presence of heterogeneous variables that may have biased the results. Thus, a prospective investigation is still needed. Moreover, we documented a different approach in the use of cidofovir among different participating centers, so many questions, such as the optimal dose and the best schedule and modality of cidofovir administration, remain unresolved.

In the multivariate analysis, stem cell source was significantly associated with a better probability of predicting CR after intravenous cidofovir, being inferior for patients receiving cord blood. We speculate that the absence of BKV-specific immunity in the donor graft may predispose the patient to a persistent BKV replication and maintain the mechanism of immune attack on the bladder mucosa during the early phase of immune recovery. On the other hand, the positive effect of a conditioning regimen containing total body irradiation on the response rate to cidofovir is not easily explained and deserves further investigation. Interestingly, the lack of resolution of BKV-HC was associated with inferior OS and higher TRM rates, confirming that vesical bleeding is also a marker of poor outcome after allogeneic HSCT [7, 35].

Overall, cidofovir was found to be safe and tolerable, with moderate to severe renal toxic effects observed in only a few patients. This finding suggests that the use of probenecid or a low-dose cidofovir schedule reduces the well-known risk of renal toxic effects caused by cidofovir. Intravesical administration of cidofovir seemed to be effective, but the number of patients was even smaller, so any conclusion appears premature at this point, including whether intravesical cidofovir represents an effective alternative to intravenous administration, especially in patients at high risk of renal complications or toxic effects [36].

In conclusion, cidofovir for the treatment of BKV-HC seems to be well tolerated and associated with resolution or significant clinical improvement. A reduction in BKV load by 1–3 logs is observed in most responding patients. Additional prospective, randomized studies are needed to confirm the efficacy of cidofovir in treating BKV-HC.

THE EUROPEAN GROUP FOR BLOOD AND MARROW TRANSPLANTATION

The EBMT centers and investigators contributing patients included in this analysis are as follows (the number of patients who underwent transplantation in each center is in parentheses): Policlinico Tor Vergata, Rome, Italy, Angela Beltrame, William Arcese (5 patients); Sant Eugenio Hospital, Rome, Italy, Andrea Tendas, Paolo De Fabritiis (5 patients); Bambino Gesù Hospital, Rome, Italy, Maurizio Caniglia, Giulio De Rossi (2 patients); Institute G. Gaslini, Genoa, Italy, Maura Faraci, Giorgio Dini (7 patients); Wroclaw Medical University, Wroclaw, Poland, Joanna Owoc-Lempach, Alicja Chybicka (6 patients); Evangelismos Hospital, Athens, Greece, Ioannis Baltadakis, Dimitrios Karakasis (5 patients); Hôpital Robert Debre, Paris, France, Jean Hughes Dalle (5 patients); Medical Park Hospitals, Antalya, Turkey, Yener Koc (5 patients); University Hospital, Basel, Switzerland, Nina Khanna, Hans H. Hirsch and Alois Gratwohl (4 patients); University Hospital, Lund, Sweden, Jacek Toporski, Stig Lenhoff (3 patients); University of Padua, Padua, Italy, Simone Cesaro, Chiara Messina (3 patients); University Hospital, Bydgoszcz, PL, Jan Styczynski, Mariusz Wysocki (3 patients); Akdeniz University Medical School, Antalya, Turkey, M. Akif Yesilipek (2 patients); Medizinische und Poliklinik II, Würzburg, Germany, Werner Heinz, Herman Einsele (2 patients); Vilnius University Childrens Hospital, Vilnius, Lithuania, Jelena Rascon (1 patient); Klinik für Knochenmarktransplantation, Idar-Oberstein, Germany, Ludwig Kraut, Axel A. Fauser (1 patient); Hopital E. Herriot, Lyon, France, Mauricette Michallet, A Thiebaut, Nicole Raus (1 patient); Hospital Clínico, Salamanca, Spain, Lucia Lopez Corral, Dolores Caballero

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