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ORIGINAL ARTICLE

High burden of BK virus-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation

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BK virus (BKV) reactivation has been increasingly associated with the occurrence of late-onset hemorrhagic cystitis (HC) after allogeneic hematopoietic SCT (allo-HSCT) resulting in morbidity and sometimes mortality. We investigated the incidence, risk factors and outcome of BKV-HC in 323 consecutive adult patients undergoing allo-HSCT over a 5-year period. BK viremia values for HC staging were evaluated, as well as the medico-economic impact of the complication. Forty-three patients developed BKV-HC. In univariate analysis, young age ($P = 0.028$), unrelated donor ($P = 0.0178$), stem cell source ($P = 0.0001$), HLA mismatching ($P = 0.0022$) and BU in conditioning regimen ($P = 0.01$) were associated with a higher risk of developing BKV-HC. In multivariate analysis, patients receiving cord blood units (CBUs) ($P = 0.0005$) and peripheral blood stem cells ($P = 0.011$) represented high-risk subgroups for developing BKV-HC. BK viremia was directly correlated to HC severity ($P = 0.011$) with a 3 to 6-log peak being likely associated with grades 3 or 4 HC. No correlation was found between BKV-HC and acute graft versus host disease or mortality rate. Patients with BKV-HC required a significantly longer duration of hospitalization ($P < 0.0001$), more RBC ($P = 0.0003$) and platelet transfusions ($P < 0.0001$). Over the 5-year study period, the financial cost of the complication was evaluated at €2 376 076 ($3 088 899). Strategies to prevent the occurrence of late-onset BKV-HC after allo-HSCT are urgently needed, especially in CBU and peripheral blood stem cell recipients. BK viremia correlates with the severity of the disease. Prospective studies are required to test prophylactic approaches.

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INTRODUCTION

BK virus (BKV) hemorrhagic cystitis (HC) is a serious cause of morbidity and mortality after allogeneic hematopoietic SCT (allo-HSCT) in patients with hematological malignancies.[1] In generally clinically silent primary infection during childhood, BKV remains in a latent state,[2] mostly in the kidneys[3] and peripheral blood leukocytes.[4] Seroepidemiological studies have shown a 90% seroprevalence among adults worldwide.[5] BKV reactivation is likely to occur during the relative or absolute immunodeficiency of aplasia and during the immunosuppressive therapy after allogeneic HSCT, although immune suppression is a prerequisite for preventing graft rejection and/or prophylaxis of graft versus host disease (GvHD).

Human BKV is an unenveloped double-stranded DNA polyomavirus, first isolated in 1970 from the urine of a renal transplant recipient with ureteral stenosis.[6] BKV nephropathy has emerged as a significant and often severe complication in kidney transplantation.[7] In the HSCT setting, the risk factors associated with BKV-HC development are allogeneic versus autologous HSCT,[8,9] myeloablative conditioning,[10–12] unrelated donor transplants,[11–13] cord blood transplantation[10] and pretransplantation BKV serology measured by a quantitative method.[14] Discrepancies are found in studies regarding other factors such as recipient age,[10,13] HLA mismatching and[1,15] GvHD.[10,16] Around half of allo-HSCT patients present BKV viruria at some point after HSCT.[8,17,18] About 5–40% of the patients subsequently develop active HC.[13,19] HC is graded according to a literature-based consensus definition:[17] Grades 1 and 2 correspond to the presence of microscopic and macroscopic hematuria, respectively; Grades 3 and 4 imply clots and severe bladder hemorrhage with renal impairment, respectively. Several studies have provided a better understanding of post-engraftment BKV-HC pathogenesis, suggesting a dual chronological process.[9] The concept of immune reconstitution syndrome with BKV acting as a trigger for immune response[20] represents a new perspective to be considered when testing preventive and/or therapeutic approaches. Standard treatment for BKV-HC has not been established yet. Supportive approaches include bladder irrigation, blood transfusions and symptomatic relief treatment; the acyclic nucleoside analog cidofovir is currently the front-line drug for BKV-HC treatment. Alternative strategies are hyperbaric oxygen therapy, leflunomide and fluoroquinolone antibiotics. In very severe cases, urological intervention such as cauterization, embolization or cystectomy may be necessary.[21]

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BKV-HC is a difficult-to-treat complication of allo-HSCT resulting in prolonged hospitalization[10] and significant morbidity, putting patients at risk of further complications. Several aspects of post-allo-HSCT BKV-HC still need to be addressed to better define the disease. Here, we analyzed the risk factors involved in the development of 43 BKV-HC. We tested the hypothesis that BKV DNA blood levels correlate with the severity of the disease. Therapeutic strategies have been examined with an emphasis on cidofovir use. Finally, the outcome has been investigated, as well as the medico-economic impact of BKV-HC.

MATERIALS AND METHODS

Patients, donors and disease characteristics

Between January 2007 and December 2011, the 323 successive patients that underwent allo-HSCT in the Lyon Hematology Department were enrolled in the study. Patient and donor characteristics as well as conditioning regimens are detailed in Table 1. I.v. fluids at 3 L/m^2 per day associated with forced alkalinized diuresis prevented toxic HC during the preparative regimen. In addition, patients treated with CY received infusions of uromitexan. The diagnosis of BKV-HC was defined by the association of hematuria with urinary symptoms and positive BKV viruria and/or viremia. BKV-HC was graded according to the criteria proposed by Bedi *et al.*[17] The onset of BKV-HC was defined as the first day of urinary symptoms associated with hemorrhagic signs and remission was considered at the last day of bleeding. The clinical characteristics of BKV-HC cases are detailed in Table 2.

BKV detection in urine and plasma samples by PCR

DNA was extracted by an automatic nucleic acid platform (Nuclisens EasyMag-Biomerieux, Marcy l'Etoile, France). BKV DNA quantification was carried out by BKV R-Gene (bioMerieux–Argene) using ABI Prism 7500 real-time PCR System (Applied Biosystems, Carlsbad, CA, USA). In this study, the highest values of BK viruria and viremia obtained during the hemorrhagic episode were collected.

BKV treatment

Therapeutic strategies used against BKV-HC were studied, focusing on i.v. cidofovir. Data regarding the use of cidofovir are detailed in Table 3. Complete clinical response implied full symptom remission. Partial clinical response corresponded to the downgrading of BKV-HC severity. Clinical failure was pronounced in cases of unchanged or worsening clinical status.

Evaluation of medico-economic burden of BKV-HC

A comparison between allo-HSCT patients with and without BKV-HC was carried out using the criteria of duration of hospitalization, number of transfused RBC and platelet units, as well as cidofovir use. The transfusion thresholds were Hb level $\leqslant$80 g/L for RBC and platelet levels $\leqslant$50 G/L in case of active bleeding or $\leqslant$20 G/L otherwise. The cost was calculated using the unit price of each criterion: €213 ($277) for each RBC unit, €341 ($443) for each platelet unit, €4698 ($6109) for 1 day of hospitalization and €2350 ($3055) for 1 g of cidofovir.

Statistical analysis

Cumulative incidences estimated the occurrence of BKV-HC over time considering death without hemorrhage as a competing event. Gender, age, underlying diagnosis, type of donor, stem cells source, HLA typing, conditioning regimen, TBI, BU administration and status of disease at transplantation were analyzed as risk factors for the development of BKV-HC. Acute GvHD $\geqslant$grade II was investigated as an associated factor in a time-dependent manner. Risk factors for the development of BKV-HC were evaluated in univariate and multivariate analysis using a Fine and Gray model. Kruskal–Wallis test was used to assess the link between maximal BK viremia and subsequent BKV-HC grade. Non-parametric Wilcoxon Mann–Whitney test was used to compare hospitalization duration and the number of transfused RBC and platelet units between patients with and without BKV-HC. Furthermore, a Spearman correlation test was computed to analyze those variables according to BKV-HC grade. Landmark analysis was used to evaluate the impact of BKV-HC on overall survival. *P*-value of less than 0.05 was considered statistically significant. The statistical analyses were performed with the R software (version 2.14.2).

Table 1. Patient and donor characteristics

Characteristics, by class	*Patients with BKV-HC*	*Patients without BKV-HC*	P-*value*
Number	43	280	
Sex (male/female)	25/18	170/110	0.975
Median age (min–max)	40 (24–64)	47.5 (17–67)	0.042*
Underlying diagnosis			
Leukemia	28	145	0.73
MDS/myelo-lympho-proliferative disorder	14	123	
Non-malignant disorder	1	12	
Number of HSCT			
First	31	212	0.7
Second or more	12	68	
Donor: related/unrelated	10/33	118/162	0.0027*
Stem cell source			
PBSC	13	111	$<$0.00001*
BM	13	141	
CBU	17	28	
HLA disparity: matched/mismatched	16/27	181/99	0.0008*
Conditioning regimen			
MAC/RIC	35/8	200/80	0.21
TBI containing/without	25/18	176/104	0.67
Bu containing/without	15/28	78/202	0.44
ATG as part of conditioning (yes/no/unknown)	32/9/2	190/81/9	0.4
Disease status at transplantation (CR or CP/AD/unknown)	28/15/0	150/125/5	0.22

Abbreviations: AD = active disease; ATG = antithymocyte globulin; BKV-HC = BK virus hemorrhagic cystitis; CBU = cord blood unit; CP = chronic phase (for CML only); HSCT = hematopoietic SCT; MAC = myeloablative conditioning; MDS = myelodysplasic syndrome; PBSC = peripheral blood stem cells; RIC = reduced-intensity conditioning. **P*-value of less than 0.05 was considered statistically significant.

Table 2. BKV-HC characteristics: onset, duration, grading, duration of hospitalization and transfusion needs

Characteristics, by class		
Onset, days after HSCT, median (range) (25th–75th percentile)	37 (9 to 361) (23 to 48)	
Onset, days after marrow engraftment, median (range) (25th–75th percentile)	10 (−427 to 343) (−3.5 to 30.5)	
Platelet count at the onset of BKV-HC (G/L), median (range) (25th–75th percentile)	27 (8 to 271) (19.5 to 78.5)	
Duration, days, median (range) (25th–75th percentile)	21 (1 to 155) (11.5 to 59.5)	
Severity		
Grade 1	13	
Grade 2	7	
Grade 3	19	
Grade 4	4	
Number of BKV loads per patient and per grade, median	*In urine*	*In blood*
Grade 1	3	1
Grade 2	4	3
Grade 3	4	4.5
Grade 4	10.5	12
Duration of hospitalization (HSCT + BKV-HC) days, median (range) (25th–75th percentile)	64 (38 to 240) (49 to 98)	
RBC unit transfusions, median (range) (25th–75th percentile)	12 (0 to 89) (6.5 to 30)	
Platelet unit transfusions, median (range) (25th–75th percentile)	20 (4 to 107) (11 to 43.5)	

Abbreviations: BKV-HC = BK virus hemorrhagic cystitis; HSCT = hematopoietic SCT.

Table 3. Characteristics of i.v. cidofovir treatment

Characteristics of therapy with i.v. cidofovir	
Proportion of treated patients	39/43 (91%)
First dose, days after bleeding, median (range)	7 (1–39)
First dose, median mg/kg (range)	5 (4–6.5)
Cumulated dose, median mg (range)	1200 (300–3375)
Duration of treatment, days, median (range)	26 (1–109)
Efficacy at 5 weeks after initiation	
Complete response	25 (64%)
Partial response	3 (8%)
Failure	11 (28%)
Toxicity	
Diminution of clearance, median mL/mn (range)	33 (0–158)

RESULTS

Incidence of BKV-HC

Three hundred and twenty-three consecutive patients received allo-HSCT between January 2007 and December 2011 with BM ($n = 154$, 48%), peripheral blood stem cells (PBSC) ($n = 124$, 38%) and cord blood unit (CBU) ($n = 45$, 14%). The use of CBU increased over the study period from 13–20% between 2007 and 2011. Forty-three (13.3%) patients developed BKV-HC during the study period (Figure 1a). The annual incidences of allo-HSCT patients developing BKV-HC from years 2007 to 2011 were 5.8%, 3.3%, 19%, 10.1% and 23.8%, respectively. The increase in BKV-HC incidence was particularly marked during the years 2009 and 2011 with subdistribution hazard ratio (sdHR) 3.4 (CI: 0.9–12.1; $P = 0.063$) and sdHR 5.2 (CI: 1.5–17.7; $P = 0.0091$), respectively (Figure 1b). The median time between BKV-HC onset and date of transplant was 37 days (range, 9–361 days) and for the majority of patients (69.8%) after engraftment. The median platelet count at the onset of BKV-HC was 27 G/L (range, 8–271). There were 13 (30.2%) grade 1; 7 (16.3%) grade 2; 19 (44.2%) grades 3 and 4 (9.3%) grade 4. The median duration of BKV-HC was 21 days (range, 1–155 days).

Risk factors for BKV-HC occurrence

The cumulative incidence of BKV-HC was 38%, 10.5% and 8.5% for CBU, PBSC and BM, respectively. In univariate analysis, young age, an unrelated donor, PBSC or CBU as stem cell source, HLA mismatching and the use of BU were associated with a higher risk of developing BKV-HC ($P = 0.028$, $P = 0.0178$, $P = 0.0001$, $P = 0.0022$ and $P = 0.01$, respectively) (Table 4). In the multivariate analysis, patients receiving CBU (sdHR 7, CI: 2.3–21.1, $P = 0.0005$) and PBSC (sdHR 4.75, CI: 1.43–15.8, $P = 0.011$) had a significant risk of developing BKV-HC when compared with patients receiving BM. Of interest, younger ages as well as an unrelated donor and HLA mismatch were not independent risk factors for BKV-HC in multivariate analysis (Table 4). Consistent with prior data, CBU transplants had a significant higher cumulative incidence at 6 months post transplant in comparison with BM transplants (37.2 vs 5.6%, respectively) (Figure 1c). In multivariate analysis, a conditioning regimen including 4 days of BU trended toward a higher risk ($P = 0.0088$) (Figure 1d).

BK viremia is a marker of severity of BKV-HC

We investigated the predictive value of BKV DNA quantification regarding the severity of HC. BKV DNA assays by quantitative PCR were performed for 39 and 38 patients in the urine and the plasma, respectively. In urines, the maximal threshold of BK viruria detection was reached for all patients on the onset of symptoms, which did not allow statistical correlation between BK viruria and the grades of BKV-HC severity ($P = 0.8$). In plasma, BKV DNA levels of grades 1 and 2 HC were not different ($P = 0.37$), which allowed us to pool these groups with a median load at 3×10^2 genome copies/mL (range, 0–1.67×10^4). The median BKV DNA loads in plasma of group 3 and 4 HC were 2.8×10^3 (range, 0–1.2×10^5) and 3×10^5 genome copies/mL (range, 1.2×10^4–4×10^6), respectively. Patients with higher viral load had most likely higher HC grade of severity ($P = 0.011$) (Figure 2). Thus, level of BK viremia is directly correlated to HC severity and a 3 to 6-log peak in BK viremia likely associates with grades 3 or 4 HC.

Therapeutic options for BKV-HC

Thirty-nine (91%) patients received i.v. cidofovir (Table 3). The median time to first dose delivery was 7 days after the onset of bladder bleeding (range, 1–39). The average starting dose of cidofovir was 5 mg/kg and the median duration of treatment was 26 days (range, 1–109). The average number of delivered doses was 4 (range, 1–8). The median cumulative dose was 1200 mg per patient (range 300–3375). By the end of the treatment with i.v.

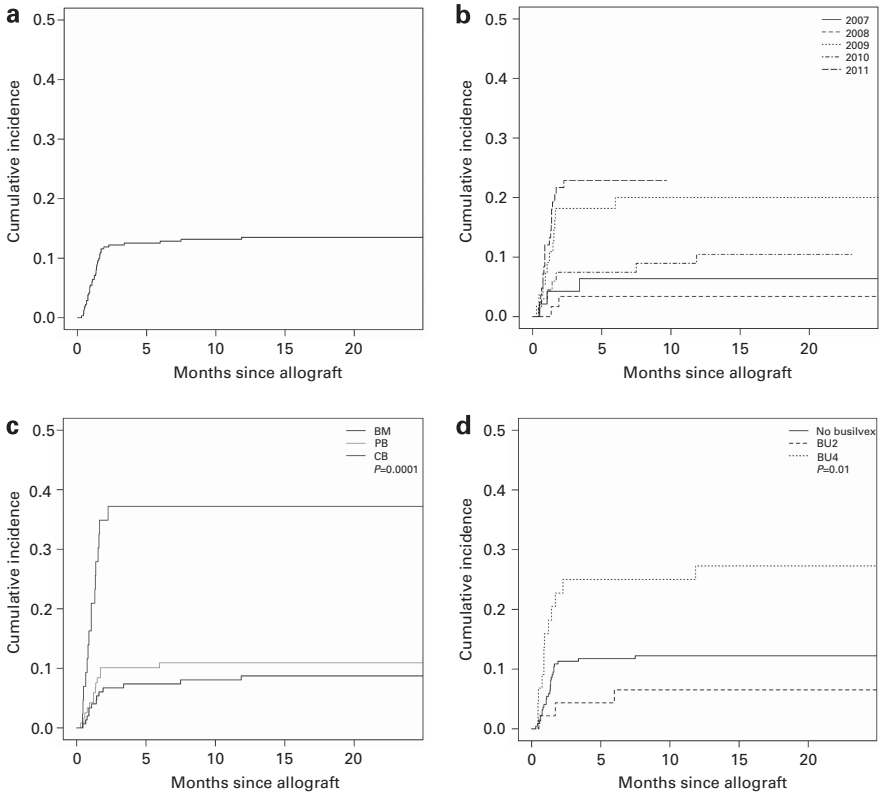

Figure 1. (**a**) Cumulative incidence of BKV-HC; (**b**) cumulative incidence of BKV-HC according to year of transplant; (**c**) to HSC source and type of donor and (**d**) according to the use of BU.

Table 4. Univariate and multivariate analysis of risk factors associated with BKV-HC

Analysis	*Univariate*	*Multivariate*		
Potential risk factor	P-*value*	*Referent*	*SdHR (95%CI)*	P-*value*
Gender: female	0.44	Male	1.13 (0.6–2.2)	0.73
Age at transplant	0.028*		0.9855 (0.96–1.02)	0.35
Underlying diagnosis	0.53		Stratification on this variable	
Status of disease at transplantation: AD	0.16	CR or CP	0.63 (0.3–1.45)	0.28
Donor: unrelated	0.0178*	Related	1.42 (0.59–3.4)	0.43
Stem cell source				
PBSC	0.0001*	BM	4.75 (1.43–15.8)	0.011*
CBU	7 (2.3–21.1)	0.0005*		
HLA typing: mismatched	0.0022*	Matched	1.1 (0.47–2.6)	0.82
Conditioning regimens				
MAC	0.3	RIC	0.37 (0.13–1.06)	0.06
TBI containing	0.91	No	1.19 (0.25–5.6)	0.82
BU containing: 2 days	0.01*	No	0.9 (0.13–6)	0.91
BU containing: 4 days			4.1 (0.8–20.6)	0.088

Abbreviations: AD = active disease; CBU = cord blood unit; CP = chronic phase (for CML only); MAC = myeloablative conditioning; PBSC = peripheral blood stem cells; RIC = reduced-intensity conditioning; sdHR = subdistribution hazard ratio. **P*-value of less than 0.05 was considered statistically significant.

cidofovir, 25 (64%) and 3 (7.7%) patients presented a complete or a partial response, respectively. No improvement was observed in 10 (23%) cidofovir-treated patients and one treated patient died from unrelated complications post-HSCT. The median decrease of renal clearance during the course of cidofovir use was 35 ml/min (range, 0–158). Cidofovir cumulative doses were not statistically associated with renal failure as assessed by a decline in renal clearance (Spearman's rho = 0.007 and $P = 0.98$). In addition, half of the patients (48%) benefited from continuous bladder irrigation. For the 13 patients with no complete response to cidofovir, clinical improvement was finally obtained with hyperbaric oxygen therapy (seven patients), instillation of alum (five patients), cauterization or embolization (seven patients) and cystectomy (one patient). Among the patients not receiving cidofovir, one was treated with oral ciprofloxacin and one had polyvalent Ig infusions with overall favorable outcome of the BKV-HC.

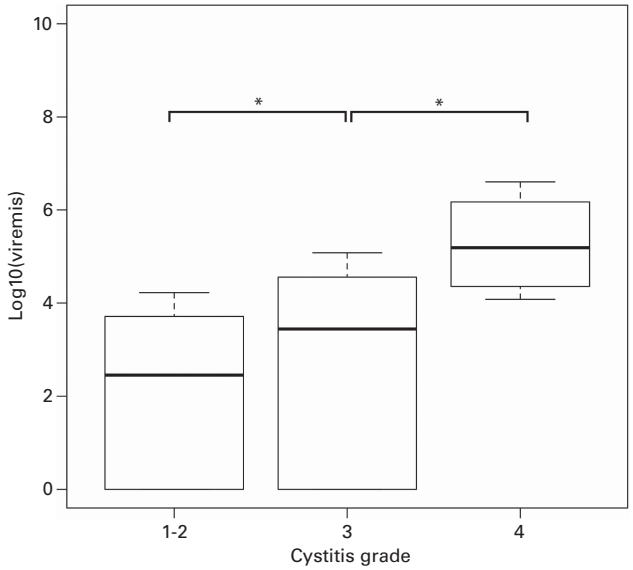

Figure 2. Relation between BK viremia and BKV-HC grading.

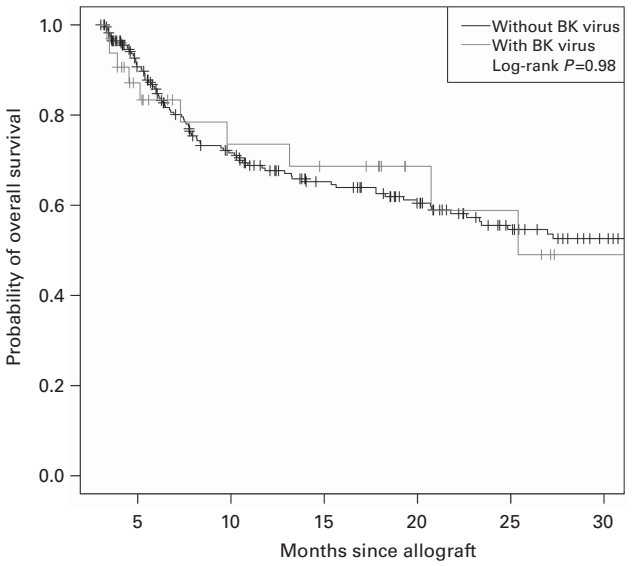

Figure 3. Probabilities of overall survival after allo-HSCT according to the presence or absence of BKV-HC.

Impact of BKV-HC on acute GvHD and survival

Six (14%) out of 43 patients with BKV-HC developed an acute GvHD (grade 2–4) after the onset of BKV-HC and conversely 9 (21%) patients developed a BKV-HC after the diagnosis of acute GvHD. When regarded as a time-dependent variable, no statistical correlation was found between the incidence of BKV-HC and acute GvHD ($P = 0.1$). However, a tight time-interval occurrence of both events is acknowledged. When comparing the allo-HSCT patients that developed BKV-HC (53.5% of whom were grades 3 and 4 HC) to allo-HSCT patients that did not develop the complication, the overall survival was not statistically different in univariate analysis ($P = 0.98$) (Figure 3).

Medico-economic impact of BKV-HC

RBC and platelet transfusions were more frequently required for allo-HSCT patients with BKV-HC in comparison with patients without BKV-HC (Figure 4a). The median number of RBC transfusions post-HSCT doubled for patients who developed BKV-HC in comparison with patients without BKV-HC (12 (range, 0–89) vs 6 (range, 0–36) RBC units; $P = 0.0003$ (Figure 4c)). The median number of platelet transfusions post-HSCT tripled for patients who developed BKV-HC in comparison with patients without BKV-HC (20 (range, 4–107) vs 7 (range, 0–60) platelet units; $P < 0.0001$ (Figure 4d)). The total cost for additional transfusion support was €245 587 ($317 743). The median duration of hospitalization for allo-HSCT was significantly longer for patients developing BKV-HC in comparison with patients without BKV-HC (50 vs 40 days; ranges, 32–167 and 19–168, respectively; $P < 0.0001$). The total cost for additional hospitalization stay was €2 020 140 ($2 626 182). The amount of transfusions and the duration of hospitalization were strongly correlated with the severity of BKV-HC ($P < 0.0001$ for all and rho = 0.61, rho = 0.58, rho = 0.69, respectively) (Figure 4b). The median cumulative dose of cidofovir delivered to patients was 1200 mg per patient, which represents a total cost of €110 349 ($142 771). Overall, the total financial cost of patients with BKV-HC over the 5-year study period was €2 376 076 ($3 088 899).

DISCUSSION

This study confirms the increase in incidence of BKV-HC post-allo-HSCT in our institution in 2009 and 2011 in comparison with 2007. In addition, we provide further insights: (i) CBU and PBSC represent high-risk subgroups of developing BKV-HC in comparison with BM transplants; (ii) the severity of BKV-HC is correlated with quantitative BK viremia; (iii) no correlation was found between BKV-HC, acute GvHD and overall survival; (iv) BKV-HC implies an important cost through transfusions, prolonged hospitalization and cidofovir use.

The pathophysiology leading to BKV-HC development is complex and multifactorial. Regarding risk factors, different studies have shown several levels of risk but CBU remains the highest risk in the HSCT settings.[10,22] In our study, CBU transplantation is the most significant risk factor for BKV-HC with a 38% cumulative incidence. Another study has previously proposed a risk stratification combining the type of donor and the HLA matching with a cumulative incidence of BKV-HC among patients receiving CBU, unrelated donor, mismatched related donor and matched related donor of 40%, 40%, 30% and 16%, respectively.[22] Another issue is the role of HLA mismatching as a cofactor for BK viruria as previously shown.[15] Although we showed that HLA mismatching and unrelated donor are cofactors in univariate analysis, multivariate analysis did not confirm it as independent risk factors. Regarding the conditioning regimen, most studies except one[1] show that MAC favors the occurrence of BKV-HC in comparison with RIC.[10–12,15,23] Our study fails to demonstrate the impact of MAC, likely attributable to the low proportion of RIC in our cohort. Moreover, the ubiquitous use of BU may also explain the lack of difference as other studies have proven BU to be a risk factor of HC development.[24–26]

As the urinary tract is the main site of BKV latency, it is expected to be the first site of reactivation. Transient BK viruria occurs in all allo-HSCT patients[19] with 4–25% of the patients developing sustained BKV-HC.[8,15,17,19,20,26–29] A peak in BK viruria $\geqslant 3$ to 6-log correlates with the occurrence of HC.[1,18,29,30] Consistent with these data, all the patients in our study had a BK viruria higher than 10^8 copies/mL indicating that BK viruria may not be the most relevant factor for the prediction of BKV-HC severity. As proposed by Bedi *et al.* and others,[17,23,31,32] BKV-HC is a three-step process, in which the last phase corresponds to hematopoietic reconstitution. This leads to uroepithelial injuries and hemorrhages, which may promote systemic dissemination through BKV release from the uroepithelial focus. Thus, BK viremia levels may correlate accurately with the clinical symptoms of HC.[1,24,33] Consistently, our data indicate that grades 3 and 4 HC were correlated with a range of 3 to 6-log peak in BK viremia. In a prospective cohort of 132 patients receiving allogeneic or

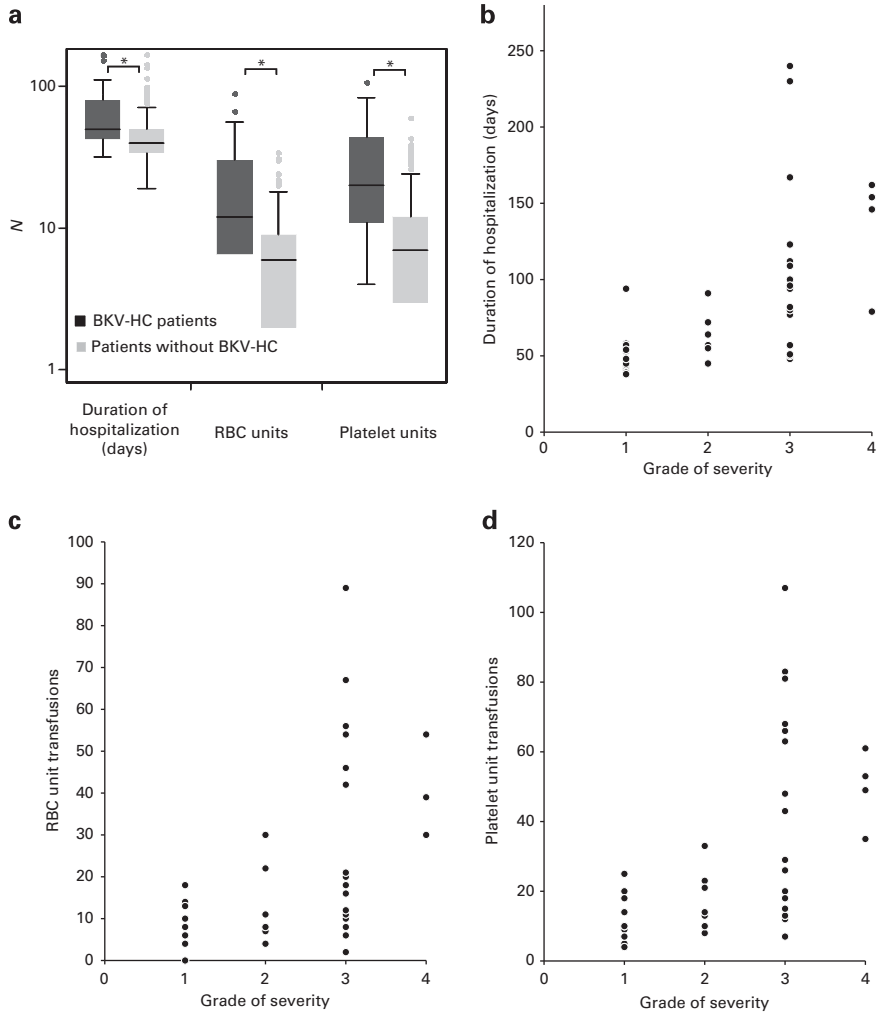

Figure 4. (**a**) Duration of hospitalization and numbers of RBC and platelet units transfused according to the presence or absence of BKV-HC; (**b**) relation between duration of hospitalization and BKV-HC grading; (**c**) amount of RBC and BKV-HC grading and (**d**) amount of platelet transfusions and BKV-HC grading.

autologous HSCT, BKV was present in 33% of HSCT recipients within the first 100 days post transplantation.[33] The authors showed a strong correlation between BKV viruria and BKV-HC and then performed a case-control study showing that patients with a BK viremia above 1×10^4 copies/mL had a significant higher risk of developing BKV-HC.[33] Finally, another recent retrospective report underscored the importance of BK viremia as a prognostic marker for BKV nephropathy in children undergoing HSCT.[34] Although most of these patients had very high BK viruria, patients with a BK viremia higher than 10^4 copies/mL had more severe BKV-associated nephropathy with an $\sim$50% survival at 1 year.[34] Thus, prospective monitoring of BK viremia on a weekly basis during the first 100 days post-allo-HSCT could be proposed.

Previous studies have suggested a causal relationship between acute GvHD and the development of BKV-HC[25,27,35] but this was not confirmed in recent studies.[1,10,11,17,22] Acute GvHD-related immunosuppressive therapy may favor viral opportunistic reactivations.[18,22] Here, when studying acute GvHD as a time-dependent variable, no correlation with BKV-HC was found.

The morbidity of BKV-HC is unanimously acknowledged. Furthermore, two pediatric cohort studies reported an impact on mortality.[34,36] A single-center study has previously documented a longer median hospital stay for patient developing BKV-HC during the first 100 days after transplant (41 vs 26 days).[10] Our findings show that BKV-HC requires a median additional 10 days of hospitalization per patient, which represents 85% of the additional cost. BKV-HC is responsible for a two-fold and three-fold increase in RBC and platelet transfusions, respectively, which represents 10% of the additional cost. Regarding the cost/efficiency of cidofovir treatment, lowering the dose from 5 mg/kg, as used in our study, to 0.5–1 mg/kg as proposed by other studies[37,38] would save 4–4.5% of the cost of this complication.

BKV-HC is an emerging viral complication post-allo-HSCT. Although BKV-HC does not enhance mortality, the morbidity of this complication remains important. In that regard, the weekly monitoring of BK viremia in high-risk patients should improve early detection of this complication. As BKV-HC optimal management is not established, prospective randomized studies evaluating the usefulness of cidofovir in BKV-HC are urgently required. The calculated additional cost reveals that BKV-HC is a financially high-burden complication. There is a need for new prophylactic and curative approaches of BKV-HC, including immunotherapeutic strategies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

LG and FA designed the study and wrote the manuscript. LG, FA, GB and NT collected the data. SM and MS analyzed the data. HLW, SDL, FB, MD, FEN, XT and MM recruited the patients. CC, TF, GS and MM reviewed the manuscript.

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APPENDIX

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