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Original Article

BK Virus-associated Haemorrhagic Cystitis in Children Undergoing Allogeneic Haematopoietic Stem Cell Transplantation: A Single Institution Experience

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Abstract

Background: BK virus-associated haemorrhagic cystitis (BKV-HC) has emerged as a serious infection after haematopoietic stem cell transplantation. The purpose of this study is to determine the incidence, risk factors, and outcome of BKV-HC. ***Procedure:*** We investigated the incidence, risk factors and outcome of BKV-HC in 207 paediatric patients undergoing first allogeneic haematopoietic stem cell transplantation over a 10-year period. BKV-HC was defined as BK virus (BKV) detection in urine by PCR testing in association with genitourinary symptoms. Thirty-three patients were tested for BKV because of symptoms indicative of haematuria during the study period. ***Results:*** Twenty-three patients were diagnosed with BKV-HC at our institution. The cumulative incidence of BKV-HC in our series was 11.1%. The median age at diagnosis was 12.8 years (range: 5.8-18.6). The median time to haemorrhagic cystitis (HC) was 22 days (range: 4-42). The dose of cyclosporine was decreased as required to maintain the graft. Most patients received myeloablative conditioning regimens (92%) and there was a trend toward higher grade of HC in cord blood transplant recipients. Univariate and multivariate analyses showed that older age ($p<0.001$) was significantly related to BKV-HC. All patients survived without sequelae except for one who succumbed to multi-organ failure. ***Conclusion:*** The majority of patients recover with conservative treatment. However, these conclusions should be regarded as preliminary in view of the retrospective and nonrandomised nature of this study.

Key words Allogeneic haematopoietic stem cell transplantation; BK virus; Haemorrhagic cystitis

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Introduction

BK virus (BKV) is considered a nephrotropic virus that establishes a persistent, harmless infection in otherwise immunocompetent individuals.[1] However, BK virus-associated haemorrhagic cystitis (BKV-HC) occurs later after transplant, usually in the post-engraftment period.[2] The clinical course of haemorrhagic cystitis (HC) following haematopoietic stem cell transplantation (HSCT) can vary from mild and brief to severe, prolonged and life-threatening.[3] Given that no standard treatment for BKV-HC has been established yet,[4] the results of our study may have important clinical implications.

Patients and Methods

Study Design

A retrospective case series design was used. The computerised database of Chang Gung Children's Hospital, a major tertiary university-affiliated hospital, was reviewed for all patients aged 0 to 18 years, who underwent HSCT between October 2006 and June 2016 and developed BKV-HC. All charts were carefully studied, and other potential aetiologies for HC were reasonably excluded. This retrospective study was approved by our Institutional Review Board, and informed consent was waived.

BKV Detection in Urine by PCR Testing

Urine samples of patients who developed HC were examined for the presence of BKV by using PCR assay. Patients with post-engraftment HC should have a BKV DNA load in urine determined at the onset of cystitis and weekly thereafter. BKV disease was defined as detection of BKV by PCR testing in association with genitourinary symptoms along with well-documented clinical course in the absence of concurrent genitourinary conditions that could influence symptom presentation. Time to BKV disease was defined as time between date of HSCT and date of first detected BKV PCR. Time to first symptoms was captured as time between date of HSCT and date of first reported genitourinary symptoms.

Therapeutic Strategies and BKV Treatment

Patient and treatment characteristics are presented in Table 1. For antimicrobial prophylaxis, cefazolin was given until the neutrophil counts exceeded 0.5×10^9/L, and oral fluconazole was prescribed for the month preceding transplantation. Voriconazole was given on the day of the transplantation and for up to 100 days. Intravenous acyclovir and oral co-trimoxazole were given to prevent cytomegalovirus (CMV) reactivation and *Pneumocystis jirovecii* infection, respectively. For patients who underwent BKV testing, we recorded reasons for testing, clinical course, imaging results, treatments, concomitant conditions, and other urinary tract infections. The subjective lower urinary symptoms were severe dysuria, frequency, urgency, and gross haematuria. BKV-HC grade was defined as described earlier:[5] grade I: microscopic haematuria; grade II: macroscopic haematuria; grade III: haematuria with clots; grade IV: macroscopic haematuria with clots and impaired renal function secondary to urinary tract obstruction.

Treatments for BKV-HC were stepwise reduction of cyclosporine (CSA) trough levels of 200-400 ng/ml to 150-200 ng/ml, and fluoroquinolone use even if BKV disease was not the main indication because of putative prophylactic efficacy. Foley catheter drainage with bladder rest may be selected for trial of spontaneous healing.

Statistical Analysis

The primary endpoint was the onset of BKV-HC. Second endpoints were treatment-related mortality and survival. A Mann-Whitney *U*-test was used to compare patients with or without BKV-HC. Risk factors for developing BKV-HC were evaluated by univariate and multivariate analysis using the Cox regression model. Values of $P<0.05$ were considered significant. Other factors considered as potential confounders in the regression analyses were recipient gender, primary haematological disease, HSCT type (unrelated versus sibling), source of stem cells (peripheral blood versus bone marrow versus cord), presence of acute graft-versus-host disease (GVHD), conditioning regimen (myeloablative versus reduced intensity), and disease status. The secondary endpoint was mortality. SPSS statistics for Windows (SPPS Inc., Chicago, IL), version 18.0, was used for these analyses.

Results

We retrospectively examined in a single-centre analysis of 207 patients who received their first allogeneic HSCT with bone marrow (n=7), peripheral blood (n=98) and

Table 1 Patient and donor characteristics

Characteristics	Patients with BKV-HC	Patients without BKV-HC	P-value
Number	23	184	
Sex (M/F)	12/11	114/70	0.497
Age in months (mean ± SE)	(151.91±40.41)	(87.64±64.99)	<0.001
Underlying diseases			
Leukaemia/MDS	13	78	
Lymphoma	0	6	
Solid tumour	0	8	
Thalassaemia	5	50	
Severe aplastic anaemia	4	19	
Fanconi anaemia	0	5	
Osteopetrosis	0	6	
Primary immunodeficiency	1	12	
Donor: related/unrelated	5/18	42/142	0.907
Stem cell source			0.931
Peripheral blood stem cell	13	85	0.155
Bone marrow	2	5	
Cord blood unit	8	94	
Human leukocyte antigen: match/mismatch	8/15	72/112	0.822
Acute GVHD in patients who engrafted			
Grade I-II	14	89	
Grade III-IV	8	53	
Conditioning regimen			
MAC/RIC	20/3	106/24	0.999
TBI-containing/without	11/12	55/129	0.098
Bu-containing/without	10/13	106/78	0.265
Antithymocyte globulin (Y/N)	18/5	150/34	0.777
Disease status at HSCT (CR or CP/AD)	10/13	105/79	0.267

AD=active disease; BKV-HC=BK virus-associated haemorrhagic cystitis; CP=chronic phase (for CML only); CR=complete remission; GVHD=graft-versus-host disease; HSCT=haematopoietic stem cell transplantation; MAC=myeloablative conditioning; MDS=myelodysplastic syndrome; RIC=reduced-intensity conditioning.

*P-value of less than 0.05 was considered statistically significant.

umbilical cord blood (n=112). Conditioning therapy consisted of a myeloablative regimen (n=180) or reduced intensity conditioning (n=27). Donor stem cell source included 42 human leukocyte antigen-identical siblings, 160 unrelated donors, and 5 phenotypically matched parental stem cells. Thirty-five (16.9%) patients were tested for BKV at our institution during the study period.

BKV-HC was diagnosed in 23 patients. The demographic and clinical characteristics of the patients who acquired BKV-HC are shown in Table 2. There was a trend for a higher incidence after myeloablative conditioning. The median age at HSCT was 12.8 years (range: 5.8-18.6). The median time to HC was 22 days (range: 4-42). There were 2 cases of grade I (9%), 10 (43%) grade II, 2 (9%) grade III, and 9 (39%) grade IV. Six of 9 grade IV cases occurred in recipients of cord blood transplants. Overall, the cumulative incidence was 11.1% at day 100 (Figure 1). The median peak of the urine BKV load was $3.6x10^8$ copies/mL (range: $5.0x10^5$-$3.1x10^{10}$). There was no direct correlation between viral load and severity grading of HC. Seven children had a concomitant CMV antigenaemia.

Seven patients required Foley catheter drainage with bladder rest. One of 7 patients also received intravenous cidofovir, and 1 patient received hyperbaric oxygen in conditions unresponsive to Foley catheter drainage greater than 10 days. The dose of cyclosporine was decreased if required. Moreover, clinical resolution of HC usually occurred earlier than negative BKV PCR. A reduction of >1 log in the BKV load was found in 22 patients, while 1 patient was treated with cidofovir but eventually died of multi-organ failure. Only older age was associated with risk of BKV-HC on univariate analysis ($p<0.001$) and remained the only significant factor on multivariate logistic regression. Clinical improvement was observed in all cases who survived.

Discussion

HC occurs in 5%-68% of patients after HSCT, and patients with HC tend to have higher peak urine viral loads and excrete much larger amounts of BKV in the urine.[6,7] Since the routine use of mesna uroprotection had significantly reduced cyclophosphamide toxicity, early-onset of HC was rarely mentioned by respondents in our study. BKV is the most important pathogen of late-onset HC after HSCT.[8,9] The pathogenesis leading to BKV-HC has not been elucidated. In competing risk analyses, BKV viruria $\geq 10^7$ copies/mL, older age, CMV reactivation and foscarnet use were risk factors for HC.[10] The urologic manifestations range from microscopic haematuria to severe haemorrhage with obstructive renal failure. However, no standard and evidence-based treatment escalation algorithm has been widely adopted yet.[4,11]

Around half of the recipients following allogeneic HSCT present BK viruria at some point after HSCT and about 5-40% of the patients subsequently develop active HC.[4,12-14] Similar to other studies, our study also found older age to be a risk factor for the development of HC in children.[14,15] However, the exact pathogenetic link between BKV and HC remains enigmatic. This leads to the speculation that the increased rate of BKV-HC with elevated CSA levels might have been mediated in part by the immunosuppression in patients with supratherapeutic CSA levels. It is essential to reduce immunosuppressive therapies in patients with BKV-HC, and most patients recover with conservative care.[16,17]

BKV-HC after HSCT is the result of a complex interaction of donor type and preparative regimen intensity. GVHD is a common complication of allogeneic HSCT. As in other study cohorts,[4,12] no correlation was found between BKV-HC and acute GVHD or mortality rate. In addition, we provide further insight: (i) older age represented a high-risk subgroup of developing BKV-HC after HSCT; (ii) no correlation was found between BKV-HC, donor source, conditioning regimen, and disease status. The majority of our patients recover through conservative management including dosage reduction of cyclosporine and prolonged Foley catheter drainage with bladder rest. In addition, hyperbaric oxygen (HBO) may benefit patients

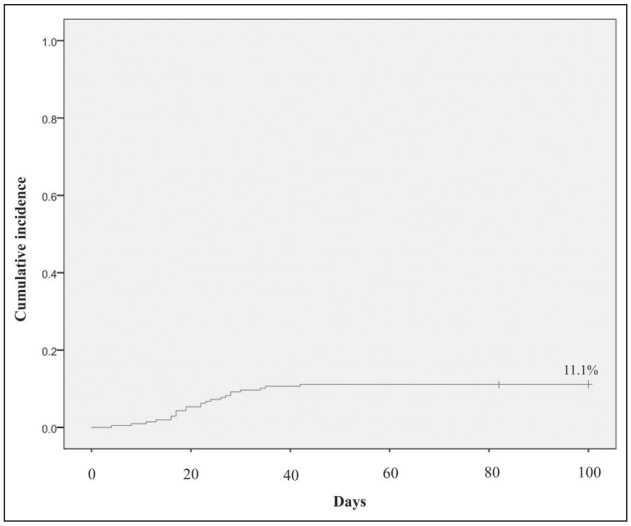

Figure 1 Cumulative incidence of BK virus-associated haemorrhagic cystitis.

Table 2 Demographic and clinical characteristics of patients with post haematopoietic stem cell transplantation BK virus-associated haemorrhagic cystitis

Pt	Sex	Age (y)	Diagnosis	Transplant Type	Conditioning regimen	Immunosuppressant	Concurrent CMV reactivation	HC Grade	Peak urine viral load$x10^3$ copies/mL	Treatment	HC outcome
1	F	13.0	Thalassaemia	Unrelated cord blood	Myeloablative	ATG + CSA + MP	Yes	IV	3925.9	CSA reduction Foley	Cure
2	M	11.9	ALL	Unrelated cord blood	Myeloablative	ATG + CSA + MP	Yes	IV	2578.1	CSA reduction, Foley, cidofovir Ciprofloxacin	Died
3	M	16.3	AML	Unrelated cord blood	Myeloablative	ATG + CSA + MP	Yes	II	62548.6	CSA reduction	Cure
4	F	16.5	SAA	Allogeneic related	Reduced intensity	CSA + MTX	No	II	23735682.6	CSA reduction Ciprofloxacin	Cure
5	F	16.5	ALL	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	Yes	II	30896564.6	CSA reduction	Cure
6	M	11.8	ALL	Allogeneic related	Myeloablative	CSA + MTX	No	II	9484685.4	CSA reduction	Cure
7	F	11.8	AML	Allogeneic related	Myeloablative	CSA + MTX	No	II	360440.6	CSA reduction	Cure
8	F	5.8	Thalassaemia	Unrelated cord blood	Myeloablative	ATG + CSA + MP	No	II	1933076.5	CSA reduction	Cure
9	F	13.5	AML	Allogeneic unrelated	Myeloablative	ATG + CSAA + MTX	No	II	180183.6	CSA reduction	Cure
10	F	10.4	Thalassaemia	Unrelated cord blood	Myeloablative	ATG + CSA + MP	No	III	692610.4	CSA reduction	Cure
11	F	15.8	ALL	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	No	I	492556.5	CSA reduction	Cure
12	F	12.7	Thalassaemia	Unrelated cord blood	Myeloablative	ATG + CSA + MP	No	IV	497.5	CSA reduction Foley, Ciprofloxacin	Cure
13	M	10.4	Thalassaemia	Unrelated cord blood	Myeloablative	ATG + CSA + MP	No	IV	664233.7	CSA reduction Foley, Ciprofloxacin	Cure
14	F	9.2	ALL	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	No	IV	165461.0	CSA reduction Foley	Cure
15	M	10.1	ALL	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	No	III	38806.1	CSA reduction	Cure
16	M	12.8	SAA	Unrelated cord blood	Reduced intensity	ATG + CSA + MP	Yes	IV	2293946.6	CSA reduction Foley, HBO	Cure
17	M	17.5	AML	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	No	IV	58617.8	CSA reduction Foley, Ciprofloxacin	Cure
18	M	9.6	AML	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	Yes	II	13983.8	CSA reduction Ciprofloxacin	Cure
19	F	17.8	SAA	Allogeneic related	Myeloablative	CSA + MTX	No	II	97676.9	CSA reduction	Cure
20	M	10.2	ALL	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	No	II	31810.9	CSA reduction	Cure
21	F	14.2	ALL	Allogeneic related	Myeloablative	CSA + MTX	No	I	898947.1	CSA reduction Ciprofloxacin	Cure
22	M	7.6	SAA	Allogeneic unrelated	Myeloablative	ATG + CSA + MTX	No	IV	2325106.8	CSA reduction Ciprofloxacin	Cure
23	M	6.0	CGD	Unrelated cord blood	Myeloablative	ATG + CSA + MP	No	IV	2276943.6	CSA reduction Ciprofloxacin	Cure

ALL=acute lymphoblastic leukaemia; AML=acute myeloid leukaemia; ATG=antithymocyte globulin; CGD=chronic granulomatous disease; CMV indicates cytomegalovirus; CSA=cyclosporine; HBO=hyperbaric oxygen; HC=haemorrhagic cystitis; MP=methylprednisolone; MTX=methotrexate; SAA=severe aplastic anaemia

with BKV-HC after HSCT.[11,18,19] HBO therapy promotes capillary angiogenesis and the healing process in damaged tissue and has been extensively evaluated in the management of adults with radiation-induced HC and cyclophosphamide-induced HC.[20-22] Fluoroquinolone antibiotics may be more effective as prophylactic agents against BKV-HC rather than therapeutic agents.[2] Cidofovir has emerged as an effective agent for the treatment of BKV nephropathy, but its use for BKV-HC in paediatric HSCT recipients has not yet been established as a standard therapy.[23]

The results of our study provide important insights as follows: firstly, most patients had received myeloablative conditioning regimens and there was a trend toward higher grade of HC in cord blood transplant recipients; secondly, the grade of BKV-HC is not correlated with quantitative BK viruria. However, a limitation of our study is that we did not measure BK viraemia. Others have shown an association between plasma viral load and development of HC.[24,25] Another limitation is the lack of information on other viruses, such as adenovirus, which can also lead to HC. Furthermore, renal biopsy is not routinely performed in such instances because the risks of bleeding seem to outweigh the benefits. The diagnosis of BKV nephropathy was based on a combination of renal biopsy to demonstrate viral cytopathic changes, urine cytology and quantitative viral load in plasma.[26]

Treatment beyond conservative approach entails higher risk for side effects, and treatment escalation proportional to HC intensity is warranted. One of the important limitations of this study was that not all patients were tested for BKV and we were uncertain whether asymptomatic patients might also carry BKV. Prospective studies are needed to better define the morbidity of BKV disease and to properly inform the impact of future prophylaxis and treatment trials.

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Conflict of Interest

The authors have no conflicts of interest or funding to disclose.

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