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Risk Factors for Haemorrhagic Cystitis in Paediatric Allogeneic Hematopoietic Stem Cell Transplant Recipients

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Abstract

Haemorrhagic cystitis (HC) results in significant morbidity among hematopoietic stem cell transplant (HSCT) recipients. Several potential causes for HC have been postulated, including viral infection, but definitive evidence is lacking, particularly in paediatric HSCT patients. Ninety paediatric HSCT recipients were prospectively tested on a weekly basis for adenovirus and BK virus by quantitative real-time PCR in blood and urine samples. Results were correlated with the occurrence of grade II-IV HC. The odds ratio (OR) of HC (95% CI) for BK virus 1×10^9 copies/mL of urine was 7.39 (1.52, 35.99), with a p-value of 0.013. Those with aGVHD also had higher odds of developing HC, with an OR of 5.34. Given a 20% prevalence rate of HC, positive and negative predictive values of 29% and 95% were seen with a cutoff of 10^9 copies/mL. BK viremia did not reach significance as a risk factor for development of HC ($p=0.06$). Only 8 patients showed adenoviruria and 7 showed adenoviremia; all had low viral loads and four had no evidence of HC. HC in paediatric HSCT is correlated most strongly to elevated urinary viral load of BK virus and to aGVHD, but less strongly to BK viremia.

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Keywords

BK virus; Bone Marrow Transplant; Hematopoietic Stem Cell Transplant; Haemorrhagic Cystitis

Introduction

Haemorrhagic cystitis (HC) represents a significant cause of morbidity in hematopoietic stem cell transplant (HSCT) patients; its incidence varying, with reports of 12 and 16% in two recent studies (1, 2) and 21% shown among paediatric patients(2). High grade HC can necessitate multiple transfusions, extended hospitalization, and result in severe pain and urinary obstruction(3). Early onset HC typically occurs pre-engraftment, usually resolves spontaneously, and is usually attributed to conditioning therapy, particularly high dose cyclophosphamide. In contrast, late onset (post-engraftment) HC typically occurs a month or more after engraftment and may follow a prolonged course(4). The causes of late-onset HC are less well-defined, and several factors may be involved. Factors that have been associated to a greater or lesser extent by various authors include graft-versus-host disease (GVHD), graft source, degree of transplant mismatch, severity of myeloablative conditioning, use of busulfan, and viral infection, particularly with adenovirus or BK virus(1, 3–6). An association between adenoviruria and HC has been noted, primarily in Japanese populations(7, 8); however, most published literature focuses on BK virus (BKV) as a potential causative factor in the development of late-onset HC.

BKV is a human polyomavirus with a high seroprevalence in adults (up to 90% in some studies). Most primary infections occur at a young age (approximately 50% seropositive by 10 years) and are either asymptomatic or associated with fever and upper respiratory tract symptoms(1, 9). Following primary infection, the virus persists in urothelial cells and can be transiently shed asymptotically in children, the elderly, and in association with pregnancy, diabetes mellitus, and immunosuppressive conditions such as HIV infection and transplantation. BKV is seen as a primary cause of nephropathy following allogeneic renal transplantation (BK associated nephropathy [BKAN]), resulting in graft dysfunction, ureteral stenosis and graft loss. While histopathologic findings are required for definitive diagnosis, increased viral load in blood or urine are predictive of BKAN, and routine monitoring, typically by real-time PCR is now standard-of-care in many settings, with elevated blood viral load tending to have a higher predictive value than increased viruria(10, 11).

The association between BKV and late-onset HC is less well-established than that with BKAN. However, several studies have shown a variable association between elevated BK viral burden in blood or urine and the development of HC after HSCT(1, 5, 6, 12–15). The majority of these studies have been in the adult transplant population, but a smaller number of investigators have examined the question in paediatric patients. Only one recently published work looked at the association between BK viremia and HC(16); however, that study did not include urinary viral loads and was limited to opportunistic testing of patients based on clinical suspicion (typically, exhibiting at least microscopic hematuria). The present study is unique in its longitudinal follow-up and prospective sampling of both blood

and urine from all eligible asymptomatic paediatric allogeneic HSCT patients at a major paediatric oncology center, with quantitative analysis of all samples for both BKV and adenovirus by real-time PCR methods.

Materials and Methods

Study Population

The study population included all children undergoing allogeneic HSCT at St. Jude Children's Research Hospital (SJCRH) from December, 2006 to May, 2012. During this period, there were 236 allogeneic HSCTs in 220 patients. Reasons for exclusion included the following factors: patient too young of an age to reliably provide serial urine collections (not eligible, 35 patients), transplant during a temporary pause in accrual for interim analysis (21 patients), patient receiving a subsequent HSCT after completion of initial participation in this study (16 transplants), lack of consent to study participation (27 patients), and enrollment on study but patient not proceeding with the planned HSCT (5 patients). The remainder (42 patients) were not enrolled for a variety of reasons, largely related to administrative and logistical issues. At the conclusion of the study, 90 patients were included for analysis (Table 1). This study was approved by the SJCRH institutional review board (IRB).

Samples

Urine samples were obtained once weekly for 15 weeks, for quantitative adenoviral and BK viral PCR and for routine urinalysis. Blood samples were routinely collected weekly for quantitative viral PCR testing as a standard of care (adenovirus PCR) and per protocol for all allogeneic HSCT for up to approximately 100 days (15 weeks) post-transplant; remnant blood from the same sample was be used for quantitative adenoviral and BK viral testing for the present study. Viral load tests were run as samples were received, in the same prospective timeframe as collection. Laboratory values for protocol driven tests were not reported to clinicians. These data were collected and stored in a password-protected computer database prior to analysis.

Clinical Data Collection and Definitions

Demographic data and information regarding underlying disease and transplant were collected on study entry, as shown in Table 1. Transplant data included whether or not anti-CD3 antibody (OKT3) or anti-thymocyte globulin (ATG) were administered and whether the graft was ex-vivo T-cell depleted. Pre-transplant lab values were recorded, including CD4+ and CD8+ T-cell counts and serum creatinine. Ongoing chart review recorded occurrence of GVHD, fluoroquinolone administration, steroid use, and treatment with other immunosuppressive medications. HC was graded according to National Cancer Institute (NCI) Criteria(17). Off-study criteria included failure to proceed with planned transplant, patient death, development of anuria, 100 days post-HSCT if not developing HC or if HC resolved prior to day 100 post-HSCT, or day of resolution of HC event if beyond 100 days post-HSCT. Other off-study criteria included graft-failure and re-transplant, disease progression or relapse requiring additional chemotherapy, voluntary withdrawal, and loss of contact with patient.

Detection of adenovirus and BK virus

A total of 647 pairs of whole blood and urine specimens were collected. DNA was extracted from 200µL of sample using the EZ1 Virus Mini Kit on a BioRobot EZ1 workstation (QIAGEN, Valencia, CA). Internal amplification control (Luminex Corp. Austin TX) was added prior to extraction to act as an extraction and amplification control. Purified nucleic acid solution was stored at -70°C until testing. The samples were tested using quantitative real-time PCR assays for detection of adenovirus and BK virus as previously described(18, 19).

Statistical Analysis

A total of 90 patients who underwent transplant were included in the analysis. The association between the factors of interest (listed in Table 2 and categorized as binary variables) and development of HC was evaluated using Fisher's exact test in a univariate manner. The relationship between urine BK virus levels and HC was evaluated using Cox's proportional hazards model and logistic regression. In Cox's proportional hazards model, time to developing HC was modeled as a function of aGvHD (Grade 3&4 vs. Grade <3) and peak BK virus load in urine (10^9 vs. $<10^9$), the factors that were significant in univariate analysis. Those who did not develop HC by day 100 were censored at day 100. In logistic regression analysis the probability of developing HC was modeled as a function of aGvHD and urine BK virus load categorized as above. The two approaches gave very similar results and the results from the logistic regression are reported. Then, using the cut-offs for the peak BK virus load in urine as described above and assuming 20% prevalence rate of HC, the sensitivity, specificity, positive predictive value and negative predictive values corresponding to these cut-offs in predicting presence or absence of HC were estimated. A parallel analysis, similar to the one described for BK virus load in urine, was conducted for BK virus levels in blood with peak BK virus load in blood categorized as >0 copies/mL vs. 0 copies/mL.

It may be noted that the association of BK viremia and viruria with HC was also examined based on mean viral load but neither blood nor urine showed an association with HC; therefore, the results corresponding to peak viral load are reported. The rate of change in viral load showed marked inconsistencies across patients and therefore was not formally evaluated.

The relationship between BK virus in urine and transplant reconstitution parameters CD4⁺ T-cell and absolute lymphocyte count was evaluated, univariately, using generalized linear model. The relationship between developing aGvHD and BK virus in urine was evaluated using Cox's proportional hazards model and logistic regression where time to developing (or developing) aGvHD was modeled as a function of peak urine cut-offs described above. The results corresponding to logistic regression are reported. A similar, parallel analysis was also undertaken for BK virus levels in blood.

Results

A total of 90 patients who underwent allogeneic transplant were included in the analysis. Patient characteristics are summarized in Table 1. The results shown in Table 2 suggest that only aGvHD was significantly associated with HC with p-value = 0.009. Other variables, including gender, race, TBI, ATG use, receipt of a T-cell depleted graft, and treatment with fluoroquinolones showed no association with HC.

Based on the logistic regression, the odds ratio (OR) (95% CI) for developing HC was 7.39 (1.52, 35.99) in patients with peak urinary BK virus load $\geq 1 \times 10^9$ copies/mL compared to those with peak viral load $< 1 \times 10^9$ copies/mL, with a p-value of 0.013. Those with aGvHD also had higher odds of developing HC, with an OR of 5.34 (95% CI 1.44, 19.90), p-value of 0.012. The sensitivity and specificity using the BK virus load cut-off of $\geq 1 \times 10^9$ copies/mL to predict the presence or absence of HC were 89%, and 46%, respectively; and the positive and negative predictive values were 29% and 95%, respectively (Table 3). Importantly, peak BK viruria was seen a median of 13 days prior to the occurrence of HC. No association was seen between development of aGvHD and BK viruria (p-value 0.4424) or between CD4⁺ T-cell count and BK viruria (p-value 0.50). A negative association was seen between absolute lymphocyte count (ALC) and BK viruria (p-value 0.0013).

BK viremia was less strongly correlated with HC. When categorized based on presence or absence of BK viremia during the study (peak BK viral load >0 vs. 0), no significant association with HC was seen (p=0.06). However, the results of logistic regression showed a trend towards association of BK viremia with development of HC. In this case, the OR (95% CI) for development of HC when BK viremia was present was 4.71 (0.97, 22.95), p-value = 0.055. Those with aGvHD again had higher odds of developing HC, OR 5.12 (95% CI 1.45, 18.12), p-value = 0.011. Presence of BK virus in the blood had sensitivity, specificity, positive and negative predictive value for HC of 89%, 37%, 6%, and 93%, respectively (Table 3). No association was seen between BK viremia and aGvHD (p-value 0.7611), CD4⁺ T-cell count (p=0.63), or ALC (p=0.48).

A significant association was seen between blood and urine BK viral loads when evaluated for the entire cohort and within subgroups of patients with and without HC (p-values <0.0001 for all three analyses). Longitudinal plotting of blood and urine viral loads also showed that they tended to track together over time, with blood viral load typically several log units below that seen in urine (Figure 1). However, the correlation was imperfect, with numerous instances of very low or negative BK viremia, while viruria continued in a given patient. This may make it difficult to use BK viremia to track patients already known to have high levels of BK viruria.

Only 8 patients had adenoviruria, two developed HC and 6 did not. Seven patients had adenoviremia, all with low viral loads ($<5,000$ copies/mL). Three developed HC, including two patients who had detectable urine adenovirus, 4 did not have HC. No further analysis was done on either group.

Discussion

Findings here add significantly to our understanding of HC in the pediatric allogeneic HSCT population. BK virus continues to show an association with HC, and a high urinary BK viral load was strongly associated with an increased risk for HC in this group, with an odds ratio of 7.39 and a negative predictive value of 95%. However, the positive predictive value was poor, limiting the utility of urine as a screening test. The presence of BK virus in blood was a poor predictor of HC compared to urine; and while the two (blood and urine BK viral loads) were correlated, the use of blood BK testing as a surrogate marker for HC was not supported by these data. No evidence of an association between adenovirus and HC was seen, but aGVHD was associated with an increased risk of HC. No other patient characteristics showed an association with HC.

Previous studies on potential viral etiologies of HC in HSCT patients have shown variable results, and few have focused on the pediatric oncology population. Certainly, some have shown increased rates of HC in adults, some in association with viruria and some viremia. As with other literature surrounding viral testing by molecular methods, these studies suffer from inconsistencies in sample type and other aspects of methodology, making comparisons difficult. While some have looked at presence or absence of virus, others have used a quantitative approach(20). In the present work, viral loads in blood were too inconsistent to determine a threshold; whereas a cutoff of 10^9 viral copies/mL of urine showed clear predictive value. Urine has been seen by others as more predictive, though cut points have varied, in some cases because 24 hour urine sediments were used, rather than the spot urine samples used here. The latter study(14) also showed an increase in median peak viruria in patients with HC, but showed no correlation between HC and BK viremia and no association between adenoviremia or viruria and HC. The link with viuria has been confirmed by other investigators studying adult populations(1, 4, 6). Studies in children have varied. At least one group showed an apparent advantage in sensitivity of urine BK viral load testing compared to blood(12). Another group looking only at plasma showed peak viral load(16) to be strongly associated with an increased risk of HC. This study was limited by design considerations however, and was potentially biased by its retrospective design(16). Other investigators, primarily (but not exclusively) studying adult Asian populations(7, 21) have shown an association between adenoviuria and HC. Non-viral associations have also been drawn including the use of myeloablative conditioning, transplant type, aGVHD, and HLA-donor mismatch(1, 3, 4, 6).

The results of the present study are supported by its prospective design and a relatively large sample size, compared to many other studies in the adult and pediatric literature. However, resource constraints still limited the sample size and a much larger, perhaps multi-institutional, study would have more power to pick up weaker associations. Similarly, we were unable to control for geographic and temporal variations. It is possible that viral and other etiologies of HC vary over time, location, and patient genetic background. A similar population tested in Japan might show a clear association of HC and adenovirus, for example. Although treating physicians were blinded to the results of study-driven testing, they were not prohibited from performing clinical testing for BK virus and treating based on the results of such testing or on clinical impressions. Finally, as noted before, molecular

testing for BK virus and adenovirus virus lacks standardization. It has been clearly shown that test results can vary based on assay, quantitative standards, or potentially other aspects of methodology(22, 23). This consideration can only be addressed by further work in the international community towards improved standardization.

Despite these limitations, results shown here may have substantial impact on care of paediatric HSCT patients. In expanding our knowledge of the risk factors for HC in this population, a more refined use of increasingly scarce resources can be made. Routine testing of blood or urine for adenovirus, as a predictor of HC is unlikely to bring benefit, with the caveat that this may vary by geographic region. Testing for adenovirus remains important to detect and treat systemic infections, as it remains an important cause of morbidity, and mortality, particularly among paediatric HSCT patients. In the case of BK virus, elevated urinary BK viral load appears to have a stronger correlation to HC than does bloodstream detection of BK virus. In the absence of other indications (such as monitoring for potential BK associated nephropathy), testing of peripheral blood for BK virus may be unnecessary in this patient group. The high rate of BK viraemia, particularly in HC negative patients, was remarkable; comparison with published studies is difficult because most do not deal with the paediatric population, many report only viruria and not viraemia, and data tend to be presented in dissimilar ways. Direct comparison among reports also suffers from lack of assay standardization and likely increases in sensitivity over the last decade of research. Viral load testing of urine detects the vast majority of HC and elevation may be seen days or weeks prior to hematuria. However, the positive predictive value of such testing remains poor; and its practical clinical utility should be carefully considered. Opportunities for intervention with agents such as fluoroquinolones at an earlier time point may be beneficial but require prospective study. Findings here contribute to our understanding of HC; further studies are needed to confirm these results. Multi-center prospective studies are likely the best hope of accruing sufficient numbers and geographic diversity to address questions raised by this work and others.

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Figure 1.

Longitudinal plotting of blood and urine viral loads over time (only observed values plotted), with blood viral loads typically several log units below those seen in urine.

Table 1

Patient Characteristics

Variable	Subgroup	N	Percent
Diagnosis	ALL	36	40.0
	AML/MDS	32	35.6
	Acute Biphenotypic Leukemia	2	2.2
	Severe Aplastic Anemia / PNH	11	12.2
	CML	1	1.1
	Bone Marrow Failure Syndrome	2	2.2
	X-linked Lymphoproliferative Disorder	1	1.1
	Lymphoma	4	4.4
	Sickle Cell Disease	1	1.1
Donor Type	Father	13	14.4
	Mother	11	12.2
	Sibling	17	18.9
	Unrelated	49	54.4
Gender	Female	43	47.8
	Male	47	52.2
Race	Other	21	23.3
	White	69	76.7
Total Body Irradiation		47	52.2
ATG		47	52.2
^a Levofloxacin or Ciprofloxacin		18	20
OKT3		15	16.7
T-cell depleted		24	26.7
aGVHD		14	15.6
Haemorrhagic Cystitis	No	71	78.9
	Yes	19	21.1

^aDefined as starting dates before HC onset date or within 104 days of HSCT without HC.

ALL, acute lymphoblastic leukemia; AML/MDS, acute myeloid leukemia/myelodysplastic syndrome; PNH, Paroxysmal nocturnal hemoglobinuria; CML, chronic myeloid leukemia; ATG, anti-thymocyte globulin; OKT3, anti-CD3 antibody; aGVHD, acute graft-versus-host disease

Table 2

Frequency Table of Patient Characteristics and HC

Variable	Subgroup	HC N(%)	No HC N(%)	Fisher's exact p-value
Gender	Female	10 (23.3)	33 (76.7)	0.80
	Male	9 (19.1)	38 (80.9)	
Race	Other	5 (23.8)	16 (76.2)	0.76
	White	14 (20.3)	55 (79.7)	
Total Body Irradiation	No	11 (25.6)	32 (74.4)	0.44
	Yes	8 (17.0)	39 (83.0)	
ATG	No	7 (16.3)	36 (83.7)	0.31
	Yes	12 (25.5)	35 (74.5)	
OKT3	No	15 (20.0)	60 (80.0)	0.51
	Yes	4 (26.7)	11 (73.3)	
T-cell depleted	No	15 (22.7)	51 (77.3)	0.77
	Yes	4 (16.7)	20 (83.3)	
aGVHD (Grade 3, 4)	No	12 (15.8)	64 (84.2)	0.009
	Yes	7 (50.0)	7 (50.0)	
Levofloxacin or Ciprofloxacin	No	13 (18.1)	59 (81.9)	0.20
	Yes	6 (33.3)	12 (66.7)	

ATG, anti-thymocyte globulin; OKT3, anti-CD3 antibody; aGVHD, acute graft-versus-host disease

Table 3

Correlation of BK Viral Load with Development of HC

Sample	BK Virus Load	Development of HC		Total
		No	Yes	
Urine	<1,000,000,000 copies/mL	33 (94.3%)	2 (5.7%)	35
	>= 1,000,000,000 copies/mL	38 (69.1%)	17 (30.9%)	55
Blood	0 copy/mL	26 (92.9%)	2 (7.1%)	28
	>0 copies/mL	45 (72.6%)	17 (27.4%)	62

HC, haemorrhagic cystitis