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Higher Incidence of Hemorrhagic Cystitis Following Haploidentical Related Donor Transplantation Compared with Matched Related Donor Transplantation

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A B S T R A C T

Hemorrhagic cystitis (HC) is a common and important complication of allogeneic hematopoietic cell transplantation (HCT). Reactivation of BK virus is its most common cause. The more intense immunosuppressive regimens administered to recipients of grafts from alternative donors have been reported to account for the increased susceptibility to HC in this population. This study compares patients undergoing HCT with either a haploidentical donor or a matched related donor, all of whom received identical immunosuppression with a post-transplantation cyclophosphamide-based regimen. The incidence of HC was significantly higher in the patients receiving a haploidentical graft ($P = .01$). The higher incidence of HC in haploidentical graft recipients is therefore directly related to the inherent immune deficiency that follows HLA-mismatched transplantation, independent of the intensity of pharmacologic immunosuppression. This finding carries significant clinical impact for the prevention and treatment of HC in haploidentical graft recipients.

INTRODUCTION

Hemorrhagic cystitis (HC) is common following allogeneic hematopoietic cell transplantation (HCT), reported in 10% to 60% of patients undergoing the procedure [1-6]. HC causes substantial morbidity, contributes to mortality, prolongs hospitalization, and raises costs [4,5]. Its manifestations range from painless microscopic hematuria to severe pain with gross hematuria and obstructive renal failure. Although mild HC generally resolves with supportive measures, severe cases may require administration of systematic antiviral agents, bladder irrigation, intravesicular installation of E-aminocaproic acid or even formalin, cystoscopy with cauterization, urinary diversion with nephrostomy tubes, or even cystectomy.

When HC occurs within 1 to 2 weeks after allogeneic HCT, it is generally attributed to cyclophosphamide (Cy) or other agents used in the conditioning regimen or for graft-versus-host disease (GVHD) prevention [6]. HC occurring beyond 3 to 4 weeks after HCT is usually attributed to BK polyoma virus [6,7] or other viruses, such as cytomegalovirus or adenovirus; however, HC is often identified at 2 to 4 weeks following HCT, which can blur this distinction. In addition, ascribing etiology based solely on timing has proven unreliable [4,6,7]. BK virus is the most common cause of HC following allogenic HCT. Approximately 90% of adults are seropositive for BK virus [8]; latent reactivation in the urothelium is common in immunocompromised patients and can lead to HC [9]. HC is generally attributed to BK virus in patients with BK viruria at the time of diagnosis of HC, although the specificity of this relationship has been called into question [9,10]. Patients shedding virus following HCT often do not develop HC, and patients with HC due to Cy or other factors can shed BK virus [10].

Aside from the toxic effects of preparative and GVHD prevention regimens and viral infections, previous chemotherapy and radiotherapy, thrombocytopenia, both extremes of recipient age, presence of GVHD, alternative (to HLA-matched sibling) graft source (ie, cord blood, unrelated donor), graft type (mobilized peripheral blood cells) and HLA-mismatch between the graft donor and recipient have all been reported as predisposing factors [1,4,6,11,12].

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Immunosuppressive regimens of varying intensity haven been used to prevent GVHD following HCT. More intense immunosuppression is commonly administered following alternative donor transplantation, in which the risk of GVHD and GVHD-related mortality is higher. The addition of high–dose post-transplantation Cy (PTCy) to standard agents, for example, has permitted the widespread successful use of haploidentical donors. A greater frequency of BK HC has been reported following matched unrelated and cord blood transplantations [1] and after haploidentical transplantation [13] compared with HLA-matched related donor (MRD) transplantations, but differences between these groups in the intensity of immunosuppression (according to the graft source), graft type (ie, marrow or mobilized peripheral blood), previous treatment, conditioning regimens, and other factors have complicated attempts to isolate the impact of graft source.

To directly analyze the impact of graft source on HC, independent of the intensity of pharmacologic immunosuppression, here we compared the incidence, severity, and timing of HC in patients receiving haploidentical related donor grafts and patients receiving MRD grafts. All of these patients received identical GVHD prevention with a PTCy-based regimen.

METHODS

Patients

We analyzed all patients undergoing haploidentical or MRD HCT at Carolinas Medical Center from March 2014 through June 2018. Patients referred for HCT lacking an appropriate HLA-identical donor routinely underwent haploidentical HCT. Cord blood transplantation was not performed, and only 7 patients underwent matched unrelated donor transplantation during the study period. All patients received an identical myeloablative regimen consisting of i.v. busulfan, with dose adjustment based on busulfan plasma level [14], and Cy or a nonmyeloablative regimen of fludarabine (Flu), Cy, and total body irradiation (TBI), followed by infusion of mobilized peripheral blood cell grafts. All patients also received an identical PTCy-based GVHD prevention regimen, which included tacrolimus and mycophenolate for GVHD prevention [15]. This investigation was approved by the Levine Cancer Institute's Institutional Review Board.

Definitions

Determination of HC was based on a clinical presentation of cystitis with hematuria. Grades I and II HC are defined by microscopic and macroscopic hematuria respectively, grade III as macroscopic hematuria with small clots and grade IV as gross hematuria with clots, clot retention, and renal failure due to obstruction [4]. All patients with a clinical diagnosis of HC had urine analyzed for the presence of BK virus by PCR. The presence of other viruses was not systematically studied.

Statistical Methods

The primary study outcome was the incidence of HC following haploidentical donor HCT compared with that of MRD HCT. Baseline patient characteristics were compared via a descriptive statistical analysis. Fisher's exact test was conducted to calculate P values for categorical variables, and the 2-sample t test was used to calculate P values for continuous variables. The probabilities of overall survival were estimated via the Kaplan-Meier method, and the differences between haploidentical donor HCT and MRD HCT were assessed via a log-rank test. The median follow-up time was estimated using the reverse Kaplan-Meier method.

The cumulative incidences of HC, GVHD, relapse, and nonrelapse mortality (NRM) were calculated in a competing–risk setting, with death from any cause as a competing event. Group comparison of incidences were determined by Gray's test. Cox regression model was conducted to evaluate risk factors for the development of HC in univariate and multivariate analysis, and the corresponding P values were calculated using the Wald chi–square test. Possible risk factors included graft source (ie, haploidentical donor or MRD), patient age, intensity of conditioning (myeloablative or nonmyeloablative), and disease status at transplantation (ie, complete remission, not in complete remission). The Cox model was also used to assess HC as a time-dependent risk factor for overall survival. All statistical tests were 2–sided, and a P value $<.05$ was considered to indicate statistical significance.

RESULTS

Patients and Donors

Between March 2014 and June 2018, 39 patients (32%) underwent MRD HCT and 83 (68%) underwent haploidentical related donor HCT. Patient characteristics were similar in the 2 cohorts in terms of age, diagnosis, disease status, and intensity of conditioning (Table 1). Haploidentical donors were younger than MRDs (median, 39 years versus 53 years; $P < .001$).

Outcomes

The median duration of follow-up time was 22 months. The cumulative incidences of acute and chronic GVHD, relapse, NRM, progression-free survival, and overall survival were similar in the 2 groups (Table 2). The cumulative incidence of HC was significantly higher in patients who received grafts from a haploidentical donor compared with those receiving grafts from an MRD (54.9% versus 25.6%; $P = .01$) (Figure 1). The cumulative incidence of grade III-IV HC was also higher in the haploidentical donor group (17.0% versus 5.1%; $P = .07$) (Figure 2). Figures 1 and 2 show similar incidences in the 2 cohorts soon after HCT, followed by increasing separation of the curves over time. In multivariate analysis of risk factors associated with HC, only receipt of a haploidentical donor graft (hazard ratio, 2.30 on univariate analysis; 95% confidence interval, 1.20 to 4.92; $P = .01$ and hazard ratio was 2.43 in the multivariate model) (Table 3) was associated with HC. Disease status at transplantation, recipient age, and intensity of conditioning regimen were not associated with the development of HC. Thirty–one of the 51 patients (60.8%) with HC had BK viruria at the time of diagnosis of HC. The incidence of HC with BK viruria at the time of diagnosis of HC was

Table 1
Baseline Patient and Donor Characteristics

Characteristic	All Patients (n = 122)	Haploidentical Donor (n = 83)	MRD (n = 39)	P Value
Donor age, yr, median (range)	44 (13-73)	39 (13-71)	53 (25-73)	<.001
Recipient age, yr, median (range)	58.5 (21-77)	58 (21-77)	60 (26-76)	.270
Diagnosis, n (%)				
Leukemia	99 (81.2)	69 (83.1)	30 (76.9)	.375
Lymphoma	21 (17.2)	12 (14.5)	9 (23.1)	
PCDs	2 (1.6)	2 (2.4)	0 (0.0)	
Conditioning regimen, n (%)				
Myeloablative	9 (7.4)	5 (6.0)	4 (10.3)	.465
Nonmyeloablative	113 (92.6)	78 (94.0)	35 (89.7)	
Disease status at HCT, n (%)				
Complete remission	80 (65.6)	53 (63.9)	27 (69.2)	.684
Not in complete remission	42 (34.4)	30 (36.1)	12 (30.8)	

PCDs indicates plasma cell disorders.

Table 2
Clinical Outcomes

Characteristic	All Patients (n = 122)	Haploidentical Donor (n = 83)	MRD (n = 39)	*P* Value
Cumulative incidence of acute GVHD, % (95% CI)				
30 d	9.8 (5.4-15.9)	12.0 (6.1-20.1)	5.1 (0.9-15.3)	.110
100 d	37.0 (28.4-45.5)	41.0 (30.3-51.4)	28.3 (15.1-43.0)	
1 yr	43.3 (34.2-52.0)	47.7 (36.4-58.2)	33.7 (19.2-48.7)	
Cumulative incidence of chronic GVHD, % (95% CI)				
100 d	2.5 (0.7-6.6)	2.5 (0.5-7.8)	2.6 (0.2-12.0)	.861
1 yr	17.2 (10.8-24.9)	15.9 (8.7-25.2)	20.2 (8.6-35.1)	
2 yr	25.5 (17.0-34.9)	25.9 (15.5-37.5)	24.7 (11.0-41.2)	
Cumulative incidence of HC, % (95% CI)				
100 d	36.9 (28.4-45.4)	42.2 (31.4-52.6)	25.6 (13.2-40.1)	.013
1 yr	39.5 (30.8-48.1)	46.0 (34.9-56.3)	25.6 (13.2-40.1)	
2 yr	44.9 (34.8-54.5)	54.9 (40.9-66.9)	25.6 (13.2-40.1)	
Cumulative incidence of HC with BK, % (95% CI)				
10 d	13.1 (7.8-19.8)	16.9 (9.7-25.7)	5.1 (0.9-15.4)	.070
30 d	18.9 (12.5-26.3)	22.9 (14.5-32.4)	10.3 (3.2-22.2)	
180 d	25.5 (18.1-33.5)	30.2 (20.6-40.3)	15.4 (6.2-28.5)	
Overall survival, % (95% CI)				
100 d	90.1 (83.3-94.3)	91.5 (83.1-95.9)	87.1 (71.7-94.4)	.777
1 yr	77.2 (68.3-83.9)	78.0 (66.9-85.7)	75.7 (58.3-86.6)	
2 yr	63.5 (52.7-72.4)	64.8 (51.5-75.3)	60.7 (41.2-75.5)	
Progression-free survival, % (95% CI)				
100 d	81.8 (73.7-87.6)	85.4 (75.8-91.5)	74.1 (57.2-85.2)	.649
1 yr	58.3 (48.5-66.9)	58.0 (45.9-68.3)	59.5 (41.7-73.4)	
2 yr	51.1 (40.6-60.7)	47.4 (34.4-59.3)	59.5 (41.7-73.4)	
Cumulative incidence of relapse, % (95% CI)				
100 d	9.1 (4.8-15.1)	7.3 (3.0-14.3)	13.0 (4.7-25.7)	.534
1 yr	28.9 (20.6-37.6)	29.3 (19.3-40.0)	27.6 (14.1-43.0)	
2 yr	36.0 (26.3-45.8)	39.9 (27.4-52.1)	27.6 (14.1-43.0)	
Cumulative incidence of NRM, % (95% CI)				
100 d	9.1 (4.8-15.0)	7.2 (2.9-14.2)	12.9 (4.6-25.5)	.957
1 yr	12.8 (7.5-19.5)	12.7 (6.4-21.1)	12.9 (4.6-25.5)	
2 yr	12.8 (7.5-19.5)	12.7 (6.4-21.1)	12.9 (4.6-25.5)	
Median follow-up, mo	21.7	21.7	21.9	.648

higher in the cohort of haploidentical donor graft recipients (30.2% versus 15.4%; $P = .07$) (Table 2) (Figure 3). In univariable Cox model neither HC ($P = .49$) nor grade III-IV HC ($P = .49$) was associated with overall survival.

Management of HC

In addition to intravenous hydration, 6 patients underwent bladder irrigation, 18 patients received fluoroquinolones (ciprofloxacin, n = 15; levofloxacin, n = 3), and 7 patients received cidofovir, 3 of whom also received i.v. immunoglobulin. All but 3 patients achieved clinical remission or a reduced grade of HC within 4 weeks of initiation of treatment.

DISCUSSION

The incidence of HC appears to be increasing with the increasingly frequent use of alternative donors, including haploidentical related donors [1,5-7,12,13]. Susceptibility to HC following HCT using alternative donors has been attributed to the greater intensity of pharmacologic immunosuppression used to prevent GVHD in these patients [1,10,16]. Noting the interaction between graft source and the intensity of pharmacologic immunosuppression, El Zimaity et al [1] found that the more intense immunosuppression used in matched unrelated and cord blood graft recipients results in increased susceptibility to HC, but suggested that this alone did not totally account for the effect of graft source.

The use of haploidentical related donor HCT, usually in combination with PTCy to prevent GVHD, continues to expand rapidly, with growing evidence of rates of severe acute GVHD, chronic GVHD, GVHD-related mortality and overall survival similar to those reported with MRDs [15,17,18]. However, in nearly all reported comparisons of haploidentical donor HCT to MRD HCT, the haploidentical donor graft recipients received PTCy with mycophenolate and a calcineurin inhibitor or in vitro T cell depletion, whereas the MRD graft recipients received a less intensive regimen of methotrexate or mycophenolate with a calcineurin inhibitor [17,18]. Along with its more intensive immunosuppression compared with standard GVHD prevention regimens, the capacity of Cy to directly cause HC further confounds analyses of these data.

Because baseline characteristics among patients in this study receiving MRD or haploidentical grafts are similar and all patients received mobilized peripheral blood cell grafts, identical myeloablative or nonablative conditioning regimens and, most importantly, PTCy-based immunosuppression, the incidence of HC directly reflects the effect of hematopoietic cell source. Furthermore, the similar incidences of GVHD, NRM, survival, and other outcomes in the 2 cohorts diminish the likelihood that unknown factors not considered in the analysis or undetected interactions might influence the results.

The higher incidence of HC in patients undergoing haploidentical donor HCT is almost certainly due to inherent deficiencies in immunity occurring after HLA-mismatched transplantation, independent of the intensity of pharmacologic (or other) GVHD prevention. The approximately 2- to 3-fold

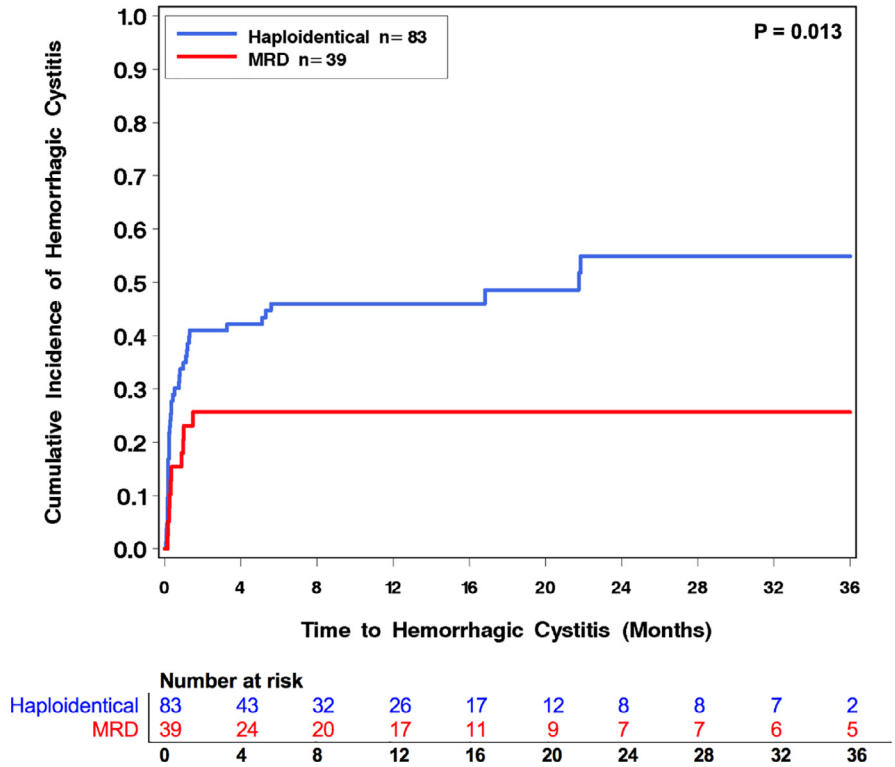

Figure 1. Cumulative incidence of hemorrhagic cystitis by graft cell source (n = 122).

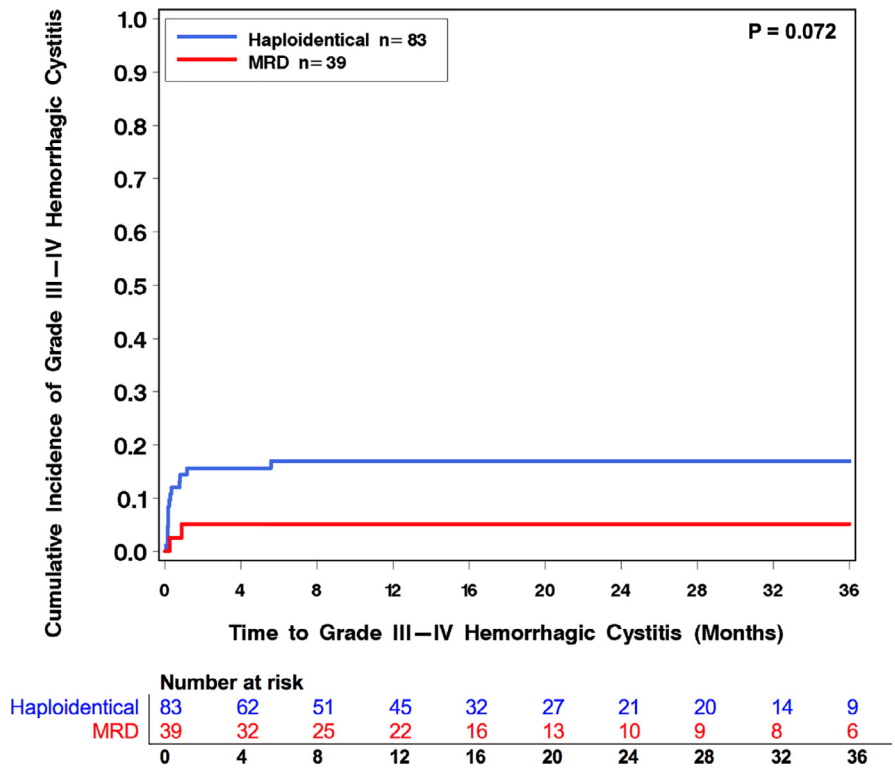

Figure 2. Cumulative incidence of grade III-IV hemorrhagic cystitis by graft cell source (n = 122).

higher proportions of recipients of haploidentical grafts experiencing BK-associated HC and grade III-IV HC suggest supportive evidence; however, as anticipated, the modest numbers of affected patients restricted the feasibility of demonstrating statistically significant differences ($P = .07$ for both). Most reports focus on delayed immune recovery following post-transplantation Cy or pan- or selective T cell depletion as the primary cause of increased susceptibility to BK and other

Table 3
Multivariate Analysis of Risk Factors Associated with HC in Patients Undergoing HCT (n = 122)

Variable	HC						HC-Grade III-IV					
	Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Allo-HCT type: haploidentical versus MRD	2.30	1.15-4.60	.018	2.43	1.20-4.92	.014	3.55	0.81-15.64	.093	3.81	0.86-16.97	.079
Conditioning regimen: myeloablative versus nonmyeloablative	1.57	0.62-3.95	.343	1.93	0.73-5.11	.184	2.07	0.47-9.13	.336	2.48	0.52-11.84	.254
Disease status at HCT: complete remission versus no complete remission	0.86	0.48-1.53	.603	0.90	0.51-1.61	.734	1.14	0.40-3.28	.811	1.17	0.41-3.38	.771
Recipient age: ≤60 yr versus >60 yr	1.16	0.65-2.04	.620	1.01	0.56-1.82	.979	1.21	0.44-3.32	.717	0.96	0.33-2.79	.944
Donor age: ≤40 yr versus >40 yr*	1.19	0.69-2.07	.530				1.03	0.38-2.77	.952			

* Donor age was significantly different between haploidentical donor and MRD at baseline, and thus was not included in the multivariate model.

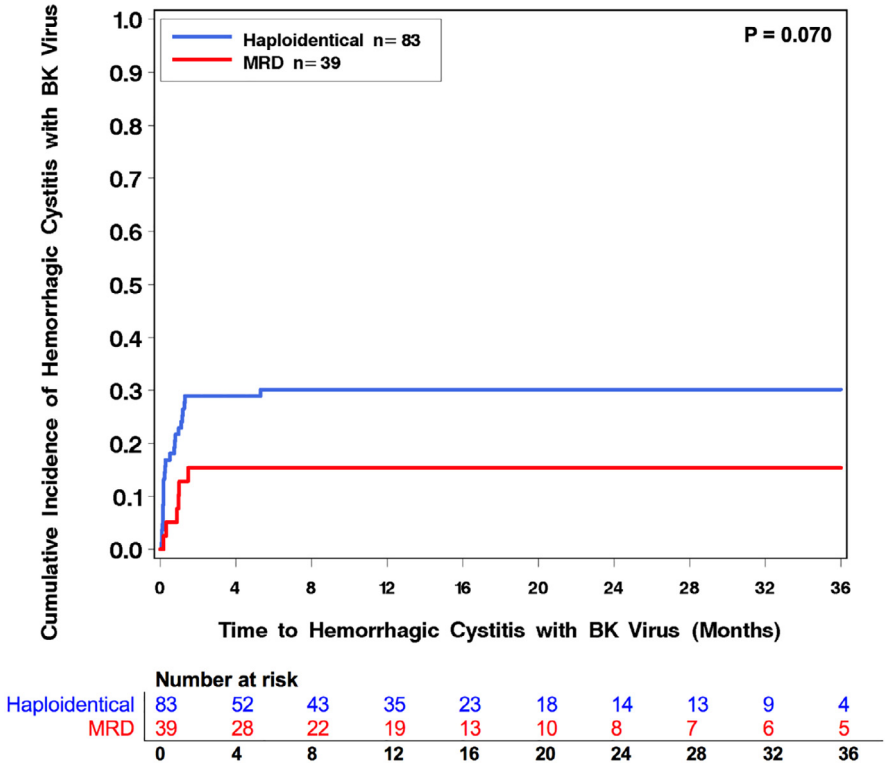

Figure 3. Cumulative incidence of hemorrhagic cystitis with BK virus by graft cell source (n = 122).

infections [19,20]. The modest incidence of HC among the MRD graft recipients in the present study supports previous evidence that patients receiving PTCy retain antiviral immunity [19-21]. Impaired cellular immunity to viruses occurs in the context of HLA disparity following mismatched grafts, because T lymphocytes are mismatched with viral antigen-presenting cells. Persistent viral antigen stimulation may result in T cell exhaustion [22], which could magnify the extent of T cell dysfunction. In addition, viruses can encode proteins sharing homology with MHC antigens that engage inhibitory NK cell receptors and dampen the NK host immune response [23], a mechanism on which recipients of haploidentical transplants rely more heavily. Similarly, the higher incidence of cytomegalovirus antigenemia among recipients of haploidentical HCT receiving differing methods of GVHD prevention [24,25] may be directly related to HLA disparity rather than, or in addition to, more intense pharmacologic immunosuppression [26]. Aside from HC, BK virus reactivation may be associated with pneumonitis, retinitis, liver disease, and meningoencephalitis in immunocompromised patients [16]. The possibility that these less common clinical manifestations of BK virus infection might occur more frequently than is currently recognized following haploidentical HCT remains largely unexplored.

This work could have significant clinical impact. While decreasing the intensity of pharmacologic immunosuppression is a common approach to treating HC, this approach may prove less effective in recipients of haploidentical donor transplants with inherently impaired antiviral immunity. Because of the limited effectiveness and toxicities of many historically available treatments, prediction or early detection of HC has not generally been emphasized. The roles of less toxic agents (eg, quinolone, leflunomide antibiotics) in prevention or early intervention remain undefined. The antiviral agent cidofovir has proven effective in severe BK HC, but with significant nephrotoxicity, [25], and its use is highly variable. Insufficient data and limited understanding of the pathophysiology of HC have led to disparate treatments [27]; innovative strategies, comparative studies, and more uniform approaches are needed.

Viral-specific T cells produced from donor cells [28] or available off the shelf [29] have proven effective in treating and preventing BK and other viral infections following HCT. In high-risk situations (eg, haploidentical transplantation), an innovative approach might include monitoring the level of BK viremia, which correlates most closely with the development of BK HC [10], and studying the value of intervention with viral-specific T cells at a predetermined threshold of viremia. Alternatively, the effectiveness of preventative administration of off-the-shelf T cells with multiple viral specificities could be studied prospectively in recipients of haploidentical transplants.

We acknowledge several limitations of this investigation. It is a retrospective single-center study, and the modest sample size limited the analyses of patients with severe HC and BK associated HC. There may have been bias in the selection of patients who lacked an HLA-identical sibling donor for haploidentical transplantation and an unrecognized imbalance between the 2 cohorts. The vast majority of patients received a nonmyeloablative conditioning regimen, which might limit the application of our results to patients receiving myeloablative conditioning. Finally, we did not systematically analyze other causes of HC, including, but not limited to, other viruses.

In conclusion, the present study provides direct evidence that haploidentical donor HCT is associated with a higher incidence of HC compared with MRD HCT, independent of the method or intensity of GVHD prevention. These results should encourage future clinical investigations designed to evaluate the effectiveness of viral-specific T cells or other approaches designed to decrease the incidence and impact of HC in this high-risk population.

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