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HEMORRHAGIC CYSTITIS AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION: RISK FACTORS, GRAFT SOURCE, AND SURVIVAL

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Abstract

Although hemorrhagic cystitis (HC) is a common complication of allogeneic hematopoietic cell transplantation (alloHCT), its risk factors and effects on survival are not well-known. We evaluated HC in a large cohort (n=1321, 2003 – 2012) receiving alloHCT from all graft sources, including umbilical cord blood (UCB). We compared HC patients with non-HC (control) patients and examined clinical variables at HC onset and resolution. Of these 1321 patients, 219 (16.6%) developed HC at a median of 22 days after alloHCT. BK viruria was detected in 90% of 109 tested HC patients. Median duration of HC was 27 days. At the time of HC diagnosis, acute graft-versus-host disease (GVHD), fever, severe thrombocytopenia, and steroid use were more frequent than at the time of HC resolution. In univariate analysis, male sex, age <20 years, myeloablative conditioning with cyclophosphamide and acute GVHD were associated with HC. In multivariate analysis, HC was significantly more common in males and HLA-mismatched UCB graft recipients. Severe grade HC (grade III–IV) was associated with increased treatment-related mortality (TRM) but not with overall survival at 1 year. HC remains hazardous and therefore better prophylaxis and early interventions to limit its severity are still needed.

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Introduction

Hemorrhagic cystitis (HC) is a serious and common complication of hematopoietic cell transplantation (HCT) affecting both allogeneic (alloHCT) and autologous (alloHCT) recipients.[1–4] Early urinary bleeding after transplant is usually attributed to toxic effects of the preparative regimens, while HC attributable to factors other than chemotherapy is usually noted more than 2 weeks after alloHCT [1]. Many factors from toxic effects of the preparative regimens to viruses have been implicated in the etiology of HC [1, 5–12]. Among viruses, polyoma BK virus, cytomegalovirus (CMV) and adenovirus are associated with HC, in both adults and children [1, 7, 13–18]. Several predisposing factors have been reported including transplant type, age at transplantation, presence of graft-versus-host disease (GVHD), donor source, and conditioning regimen components and intensity [1, 12, 19–21]. The effect of HC on survival remains controversial, but its morbidity can be substantial, even in survivors [10, 22].

We analyzed HC in a large cohort, including pediatric and adults, from one center. This large consecutive alloHCT cohort provided an opportunity to evaluate HC incidence and to define its risk factors in all age groups and among different graft sources. We also compared factors, including platelet count and coagulation tests, between HC onset and HC resolution to evaluate clinical factors contributing to the severity and duration of HC.

Patients and Methods

In this retrospective analysis, we reviewed the records of 1321 consecutive patients (787 male and 534 female) who underwent alloHCT at the University of Minnesota between July 2003 and March 2012. Patients were consented and treated according to protocols approved by the University of Minnesota Institutional Review Board and registered at clinicaltrials.gov. Of these 1321 patients, 219 (16.6%) developed HC. This subset was evaluated in detail to determine factors associated with development, and resolution, of HC.

We examined the University of Minnesota Blood and Marrow Transplant Program Database and available medical records to determine the following potential risk factors in those with HC and controls: sex, age, diagnosis and risk category, graft source and cell dose, conditioning regimen intensity, GVHD prophylaxis and ATG usage. The records of patients who developed HC were further reviewed to identify contemporaneous factors present within ± 7 days of the onset and resolution of HC including platelet count, international normalized ratio (INR), partial thromboplastin time (PTT), fibrinogen, creatinine, presence of GVHD, use of steroids, presence of fever, grade and duration of HC. Viral testing, in particular BK virus in urine and/or blood, was done at the discretion of treating providers.

Patients who underwent a reduced intensity conditioning (RIC) regimen generally received cyclophosphamide (50mg/kg IV on day −6), fludarabine (40mg/m2 IV daily from days −6 through −2) and total body irradiation (TBI, 200cGy on day −1) or fludarabine (30mg/m2 IV daily from days −6 through −2) and busulfan (3.2mg/kg IV daily on days−5 and −4). Equine anti-thymocyte globulin 15mg/kg IV every 12 hours for six doses was added for patients (n=324) who had received no multiagent chemotherapy within 3 months of

alloHCT. RIC and UCB recipients received GVHD prophylaxis with cyclosporine (from day −3 to +100) and mycophenolate mofetil (from days −3 to +30). Myeloablative conditioning (MAC) most often consisted of cyclophosphamide (60 mg/kg intravenously daily for 2 days) and 1320 cGy TBI given divided in 8 fractions. The remaining group mainly received busulphan, fludrabine, and melphalan containing regimens.

Definitions

Patients were determined to have HC based on clinical presentation of cystitis, which was further classified by grade of hematuria. Thus, grade of HC was defined according to the following criteria: Grade 1 is defined as microscopic hematuria; Grade 2 as macroscopic hematuria; Grade 3 as macroscopic hematuria with small clots; and Grade 4 as gross hematuria with clots, clot retention and renal failure due to obstructive nephropathy [15, 19, 23]. Patients were evaluated for HC from initiation of conditioning regimen through follow-up period.

Based on frequency of maximum HC grade, a grade variable was defined to compare Grade 1–2 versus Grade 3–4. HC resolution was determined once patients had 2 consecutive weeks without hematuria confirmed by urinalysis (UA). Clinical factors (including steroid use, GVHD) were considered present if active within ±7 days of HC onset or resolution.

Graft source and matching was defined as matched (HLA 8/8 allele matched) versus mismatched, bone marrow/peripheral blood stem cell (BM/PBSC) and UCB matched (HLA 5–6/6 locus matched) versus mismatched (HLA 4/6)[24, 25].

Standard disease risk includes acute leukemia, lymphoma and other malignancies in first or second remission or chronic phase CML. All other patients were defined as high risk.

Supportive care

For prevention of hemorrhagic cystitis patients receiving cyclophosphamide also received Mesna at the mg equalivalent total dose of cyclophosphamide, divided in 5 doses given 15 minutes before and 3, 6, 9 and 12 hours after each dose of cyclophosphamide. In addition, patients receive hydration at 2000 – 3000 ml/m2/day, beginning 12 hours prior and continuing 24 hours after completion of cyclophosphamide. Infectious prophylaxis, other supportive care measures, and GVHD prophylaxis have been described.[24, 26, 27]

Statistical Methods

Data on transplantation patient characteristics, post-transplantation complications and outcomes were prospectively collected by the Biostatistical Support Group at the University of Minnesota using standardized procedures. Patient and disease characteristics were summarized using descriptive statistics. Statistical comparisons of these variables between HC and control group as well as between the onset of HC and resolution of HC were completed by the nonparametric Wilcoxon test for continuous factors and Pearson chi-square test for categorical factors. Adjustments for multiple comparisons were done with Bonferroni's method. All patients were followed longitudinally until death or last follow-up. The end points included overall survival (OS) and treatment-related-mortality (TRM) at 1

year. Kaplan-Meier was used to estimate OS [28]. Cumulative incidence was used to estimate TRM [29] with relapse as a competing risk. Statistical comparison of OS between HC and the control group was completed by the log-rank test. The proportional hazards model of Fine and Gray was used to assess the independent factors associated with TRM [30]. Factors considered in multivariate analysis (MVA) were: HC severity (control vs. HC grade 1–2 vs. HC grade 3–4), cell source (matched BM/PBSC, mismatched BM/PBSC, matched UCB, mismatched UCB), disease risk (standard vs. high) and graft cell dose adjusted for graft source, gender, recipient CMV serostatus, age (0–20 vs. 21–40 vs. >40 years), conditioning (MA vs. RIC), T cell depleted (yes vs. no), and ATG use (yes vs. no). All statistical analyses were performed with Statistical Analysis System software version 9.3 (SAS Institute, Inc., Cary, NC) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

Results

HC occurred in 219 of the 1321 alloHCT patients (16.6%) at a median of 22 days (range −7 to 786 days; 25–75 percentile 16–50 days) after alloHCT and within 100 days in 193 (88%) cases. Maximum grade of HC was 1–2 in 96 patients (44%) while grade 3–4 was seen in 123 patients (56%). Median duration of HC was 27 days (range 4–105 days; 25–75 percentile 11–45 days). CMV reactivation within 100 days of alloHCT was 31% in HC patients at a median of 41 days (range 1–99 days; 25–75 percentile 27.5–49.5 days) after transplant. In HC patients, BK viruria was detected in 90% (n=109 tested), adenovirus in 2% (n=88 tested), and HHV6 in 11% (n=36 tested).

Patient demographics for both the HC and the control group are presented in Table 1. In univariate analysis, HC was more common in males, in patients age 0–20 years, in patients with non-malignant disease or with high risk malignant disease, in patients receiving myeloablative conditioning including cyclophosphamide, in patients with acute GVHD, and in patients without CMV reactivation. When age was analyzed by decades of life, patients 10–20 years (12% of control vs. 26% of HC patients) and 30–40 years (7.8% of controls vs. 13.2% of HC patients) had more HC while patients >50 years old had less HC (33.2% of controls vs.16% of HC patients). In multivariate analysis (conditioning regimen and GVHD were not included because of confounding with age and graft source). Male patients and patients receiving MM UCB transplantation (HR; 1.46; CI95%:1.06–2.00, p=0.02) had a higher frequency of HC.

Clinical factors within ±7 days of the onset and the resolution of HC are shown in Table 2. 58 patients died between and thus were not evaluable at resolution of HC. At the onset of HC, more patients had acute GVHD, fever, thrombocytopenia, and steroid therapy than at the time of HC resolution. Creatinine level was similar at onset and resolution of HC (0.8 mg/dL, range 0.2–5.1 mg/dL vs. 0.9 mg/dL, range, 0.2–3.0 mg/dL). There was no correlation between INR, PTT, and platelet counts and severity of HC at the time of HC onset. GVHD and CMV reactivation preceded the onset of HC in 50% and 13% of patients, respectively. Therapy of HC included IVF (45%), bladder irrigation (12%), and cidofovir (6%), and 37% of patients had no additional therapy. Eighty-nine percent (89/100) of patients receiving IVF, 75% (61/82) of patients receiving no therapy, and 63% (7/11) of

patients receiving cidofovir had resolution of HC whereas HC resolved in only 26% (7/26) of patients who underwent bladder irrigation.

At 1 year, OS for all patients was 65% (63–68%) and was similar for HC patients [63% (57–69%)] and controls [66% (63–69%)], p= 0.75 (Figure 1). In multivariate analysis, severe grade HC (Figure 2) and HLA-mismatched status, regardless of graft source, were associated with increased TRM (Table 3). HLA-mismatched status, regardless of graft source, was associated with inferior OS (Table 3). Patients-, disease-, transplantation-characteristics were similar between severe and non-severe HC (Table 4).

Discussion

We examined the clinical risk factors for HC after alloHCT, with emphasis on factors contributing to the development and severity of HC. HC incidence was 16.6%, in line with other studies.[8, 10, 31] Interestingly, compared to our prior study performed nearly 20 years ago, the incidence of HC has not changed.[20] Male gender was the most important risk factor for developing HC as has been reported in earlier studies of relatively small number of patients [14, 31–33].

Conditioning regimen is an important factor in development of HC and its mechanism has been well described [34–41]. In our study we found that conditioning regimens including cyclophosphamide increased HC risk. We also showed that cyclophosphamide in MAC was more frequently associated with HC compared to RIC containing cyclophosphamide. This might have resulted from the higher dose of cyclophosphamide [42] or higher doses of TBI in MAC [43]. Some studies found no relation between dose of cyclophosphamide [19, 31, 44, 45] or interaction with TBI. Conditioning regimen intensity has also been studied and MAC has been reported to induce with higher frequency of HC [1, 8, 10, 22, 39, 46, 47]. It was argued that MAC induced more HC in part due to increased risks for BK viruria [47]. In our study, BK viruria was frequent in HC patients regardless of conditioning intensity.

HC incidence is higher in unrelated donor transplantation (URD) [14, 31, 48]. In a study, HC patients received more URD transplantation (81%) than MRD transplantation (19%), p<0.05. [47] URD transplantation was reported as an independent risk factor for HC in children as well as adults.[31] HC occurred in 16% of patients receiving MRD transplants, 30% of recipients of mismatched related (MMRD), and 40% of matched URD or UCB transplants (HR 2.9 for the comparison of MRD versus URD).[21] UCB transplantation was noted as risk factor for BK virus positive HC [40], in whom the cumulative incidence of HC can be as high as 41.8% at 1 year [49]. One study showed that UCB or haploidentical donor transplantation had much higher risk for HC if BK virus was positive before alloHCT.[1] These findings may be attributed to greater and longer lasting immunologic and hematologic suppression leading to a higher risk of HC [8, 21, 31, 47]. In our study, we found that neither HLA mismatched status nor graft source alone, but that HLA-mismatched UCB transplantation was significantly associated with higher risks of HC.

Age was found to be risk factor for HC. [19, 21, 33, 46] Older age in pediatric population and younger age in adult population seem to be associated with HC.[17, 19, 21, 33, 39, 50, 51]

Although age was not significant in MVA, patients in the 2nd and 4th decades of life had increased incidence of HC. Seber et al, reported a higher incidence of HC occurring among patients age 10–30; greatest in the 10–20 year age group compared to patients vs. age <10 years [19]. Similarly, El-Zimaity et al found that age < 26 years was significantly associated with HC; an effect that was consistent across graft types [21].

The association between HC and GVHD has been studied, but remains unclear [1, 10, 19, 31, 32, 40, 48, 50, 52, 53]. Our study identified GVHD as a significant clinical variable associated with HC and fewer patients had active GVHD at the resolution of HC compared to onset. Other studies have identified GVHD as a risk factor for the development of HC; especially severe or late-onset HC [10, 19, 22, 32, 40, 41, 54, 55]. However, it remains unknown whether GVHD targeting bladder epithelium manifests as HC or whether immunosuppression from acute GVHD and/or concomitant steroid use contributes to HC and its severity [19, 56, 57]. Acute GVHD preceded HC in only half of the HC patients; however, steroid use and acute GVHD were more frequent at the onset of HC than the resolution of HC. Bogdanovic et al suggested that the combination of acute GVHD and BK virus predicted development of HC better than acute GVHD alone[14]. BK virus was frequently found to be a risk factor for HC [1, 8, 10, 40]. In this retrospective analysis, we did not aim to identify the precise role of BK virus in HC development given that BK viruria can be asymptomatic in up to 50% of alloHCT patients and that BK virus was not routinely tested at predetermined time points after alloHCT regardless of symptoms. Nearly all our tested HC patients had BK viruria. BK viruria was not associated with HC severity. We identified no significant association between adenovirus, HHV-6 or CMV in HC patients comparing the onset and resolution of HC. Some studies have associated CMV reactivation with HC [10, 22], suggesting that DNA viruses such as CMV can induce BK virus replication.[58, 59]. Our study also found that CMV reactivation rate was similar between control and HC group and that CMV only preceded HC in 13% of all HC patients.

We also evaluated clinical factors differing between the onset and resolution of HC. We found that the resolution of HC is associated with increased platelet counts. Brugieres et al describe thrombocytopenia at onset for all patients who developed HC (n=19) [39]. It is recommended that platelet counts should be maintained above 50×10^9/L [15, 39, 60] in patients with active HC. However, in 2 small series delayed platelet engraftment was not found to be a significant variable in the development of HC [21] or in children with severe HC [31]. We also analyzed serum creatinine because of its association with platelet dysfunction [61] and BK virus-induced nephropathy [62, 63], but observed no relation to risks or severity of HC. Uhm et al found worsening renal function during HC, but concluded that this resulted from concurrent CMV therapy rather than direct nephrotoxic effect of HC[10]. With respect to HC resolution and its therapy, bladder irrigation resulted in less resolution of HC, which most likely indicates that patients requiring invasive procedures had more severe-intractable HC, and thus poorer outcomes.

HC remains frequent and troublesome in particular when it is severe; often causing prolonged hospitalization, resource use and expense. The significance of HC grade I in BMT patients is not too clear. Attention in high risk patients to aggressive protection from both conditioning toxicity and virus associated HC is still important to limit its morbidity.

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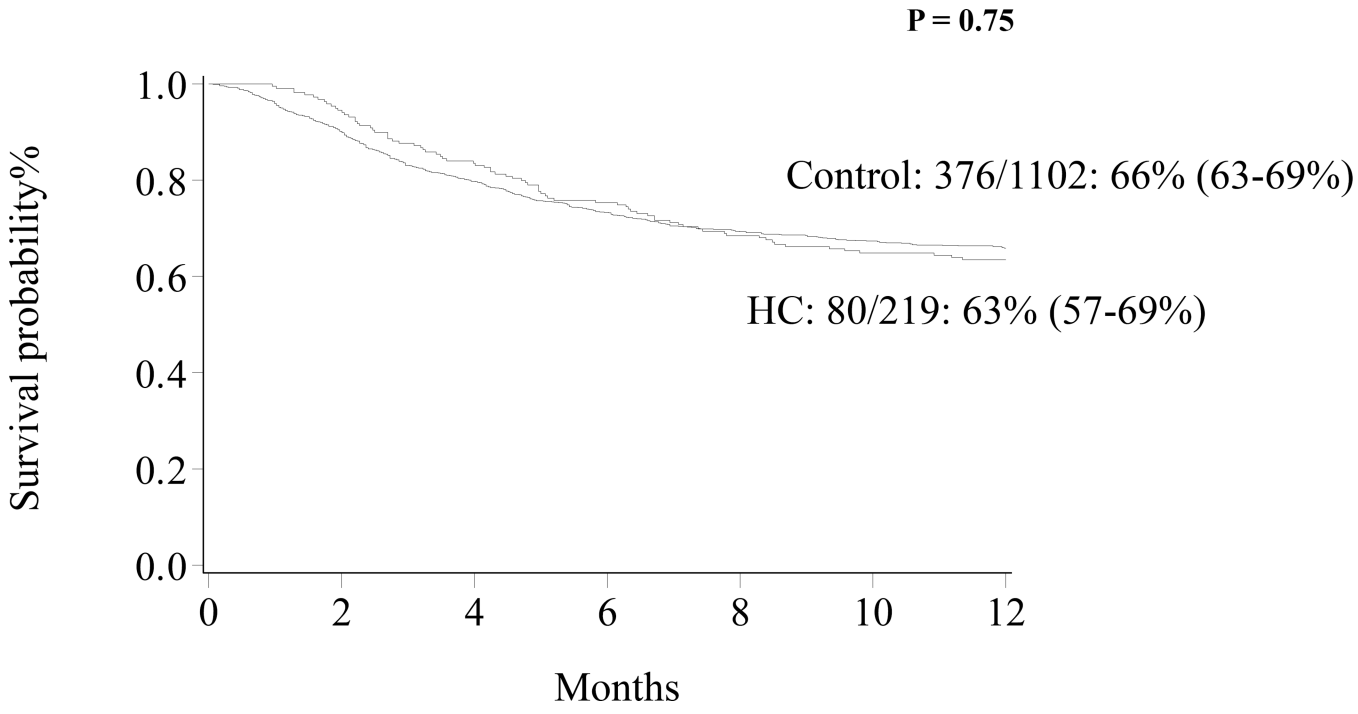

Figure 1.
Overall survival patients with HC and control.

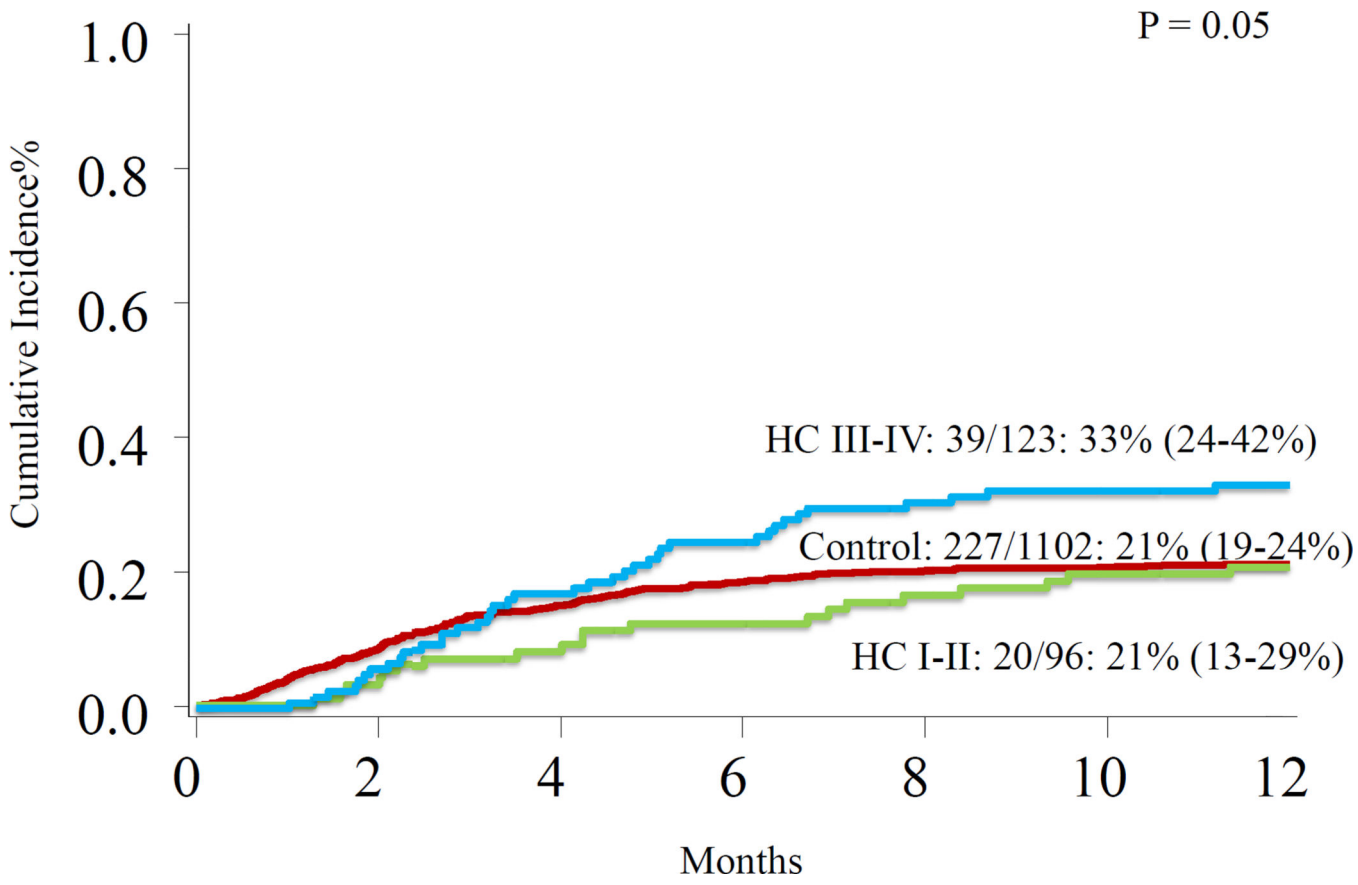

Figure 2.
Treatment-related mortality among control patients, patients with grade I–II HC, and patients with grade III–IV HC.

Table 1

Patient characteristics and risk factors associated with hemorrhagic cystitis

	Control (n=1102)	HC (n=219)	P-value (UVA)	Multivariate Adjusted Odds Ratio (95% CI) (n=219)	P-value (MVA)
Gender			<0.01		0.01
Male	640 (58.1%)	147 (67.1%)		1.00	
Female	462 (41.9%)	72 (32.9%)		0.67 (0.49–0.92)	
Median Age, in years (range)	36.5 (0.1–75.1)	20.8 (0.5–71.7)	<0.01		
Age ranges, in years			<0.01		
[0–20]	411 (37.3%)	109 (49.8%)			
[21–40]	176 (16.0%)	46 (21.0%)			
>40	515 (46.7%)	64 (29.2%)			
Disease Risk			0.04	Not included in MVA	
Non-malignant	267 (24.2%)	70 (32.0%)			
Standard Risk	437 (39.7%)	73 (33.3%)			
High Risk	398 (36.1%)	76 (34.7%)			
Donor and Graft Source			0.08		
Matched BM/PBSC	453 (41.1%)	76 (34.7%)		1.00	
MM BM/PBSC	84 (7.6%)	15 (6.9%)		1.07 (0.58–1.94)	0.84
Matched UCB	90 (8.2%)	13 (5.9%)		0.87 (0.46–1.64)	0.67
Mismatched UCB	475 (43.1%)	115 (52.5%)		1.46 (1.06–2.00)	0.02
Conditioning Regimen			<0.01	Not included in MVA	
MAC: CY	514 (46.6%)	149 (68%)			
RIC: CY	479 (43.5%)	54 (24.7%)			
No CY (RIC or MAC)	109(9.9%)	16 (7.3%)			
GVHD at 100 days				Not included in MVA	
Grades II–IV	358 (34%)	92 (43%)	0.01		
Grades III–IV	142 (13%)	47 (22%)	<0.01		

	Control (n=1102)	HC (n=219)	P-value (UVA)	Multivariate Adjusted Odds Ratio (95% CI) (n=219)	P-value (MVA)
CMV Reactivation			0.25	Not included in MVA	
No	805 (72.8%)	151 (69.0%)			
Yes	300 (27.2%)	68 (31.0%)			

Abbreviations: GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MM, mismatched; MVA, multivariate analysis; RIC, reduced-intensity conditioning; UCB, umbilical cord blood transplantation; UVA; univariate analysis.

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Table 2

Clinical variables at onset and resolution of hemorrhagic cystitis

	N	Onset (n=219)	N	Resolution (n=161)*	P-value
Platelet count (× 10^9 xL)	219	31000 (3000–311000)	161	51000 (3000–373000)	<0.01
Median (min-max)					
$25^{th}/75^{th}$ percentile		17000/51000		27000/110000	
INR (s) Median (Min-Max)	174	1.13 (0.75–1.83)	68	1.10 (0.86–1.80)	0.06
$25^{th}/75^{th}$ percentile		1.04/1.27		1.025/1.19	
PTT (s) Median (Min-Max)	81	35 (22–184)	30	32 (21–70)	0.25
$25^{th}/75^{th}$ percentile		31/42		29/38	
Steroids	207		152		<0.01
Yes		66 (30.1%)		27 (16.7%)	
No		141 (64.4%)		125 (77.6%)	
Acute GVHD	210		150		0.04
Yes		68 (31.1%)		33 (20.4%)	
No		145 (66.2%)		117 (72.6%)	
Fever	206		158		<0.01
Afebrile		119 (54.3%)		156 (96.8%)	
Febrile		87 (39.7%)		2 (1.2%)	
Creatinine (mg/dL)	219		161		
Median (Min-Max)		0.8 (0.2–5.1)		0.9 (0.2–3.0)	0.12
$25^{th}/75^{th}$ percentile		0.57/1.26		0.62/1.26	
BK Viruria	109		2		0.64
Positive		98 (44.7%)		2 (0.9%)	
Negative		11 (5.0%)		0	
CMV	218		143		0.24

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	N	Onset (n=219)	N	Resolution (n=161)*	P-value
Positive		12 (5.5%)		11 (6.8%)	
Negative		206 (94.1%)		132 (81.9%)	
Adenovirus	88		23		0.47
Positive		2 (0.9%)		0	
Negative		86 (39.3%)		23 (14.2%)	

Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease; MAC, myeloablative conditioning; MM, mismatched; MVA, multivariate analysis; RIC, reduced-intensity conditioning;; UCB, umbilical cord blood transplantation; UVA; univariate analysis.

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Table 3

1 year overall survival and treatment-related mortality by multivariate analysis in patients with HC

	OS			TRM	
Parameter	**Class**	**Hazard Ratio CI 95%**	**P-value**	**Hazard Ratio CI 95%**	**P-value**
HC Group	Control	1.00	0.14	1.00	
	Grade I-II	0.76 (0.52-1.11)		0.91 (0.59-1.42)	0.69
	Grade III-IV	1.20 (0.90-1.61)		1.52 (1.10-2.10)	0.01
Graft source	M BM/PBSC	1.00	<0.01	1.00	
	MM BM/PBSC	2.60 (1.90-3.55)		2.28 (1.53-3.41)	<0.01
	M UCB	1.14 (0.77-1.68)		1.34 (0.85-2.12)	0.21
	MM UCB	1.53 (1.25-1.89)		1.43 (1.10-1.87)	0.01

Covariates tested in UVA were: ATG, sex, age, disease risk, conditioning regimen intensity

Abbreviations:BM, bone marrow; CMV, cytomegalovirus; HC, hemorrhagic cystitis; M, matched; MM, mismatched; PBSC, peripheral blood stem cell; UCB, umbilical cord blood.

Table 4

Characteristic between grade I-II HC vs. III-IV HC

	HC Grade I-II	HC Grade III-IV	P-value
Gender			0.39
Male	59 (64%)	85 (70%)	
Female	33 (36%)	37 (30%)	
Source			0.57
M BM/PBSC	32 (35%)	43 (35%)	
MM BM/PBSC	6 (7%)	8 (7%)	
M UCB	8 (9%)	5 (4%)	
MM UCB	46 (50%)	66 (54%)	
Age Group			0.27
0–20	48 (52%)	56 (46%)	
21–40	15 (16%)	31 (25%)	
41-	29 (32%)	35 (29%)	
Disease Risk			0.23
Non Malignant	33 (36%)	35 (29%)	
Standard Risk	33 (36%)	39 (32%)	
High Risk	26 (28%)	48 (39%)	
CMV			0.50
Positive	4 (5%)	8 (7%)	
Negative	87 (96%)	114 (93%)	
BK Virus			0.46
Positive	37 (88%)	60 (92%)	
Negative	5 (12%)	5 (8%)	
Conditioning			0.77
MAC: CY	60 (65%)	85 (70%)	
RIC: CY	25 (27%)	28 (23%)	
NO CY	7 (8%)	9 (7%)	
DAH			0.20
Yes	2 (2%)	7 (6%)	
No	90 (97%)	115 (94%)	

Abbreviations: BM, bone marrow; CMV, cytomegalovirus; Cy, cyclophosphamide; DAH, diffuse alveolar hemorrhage; HC, hemorrhagic cystitis; M, matched; MAC, myeloablative conditioning; MM, mismatched; PBSC, peripheral blood stem cell; RIC, reduced-intensity conditioning; UCB, umbilical cord blood.