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Hemorrhagic Cystitis Following Allogeneic Hematopoietic Cell Transplantation

We conducted a retrospective study to investigate the incidence, risk factors, and clinical features of hemorrhagic cystitis (HC) following allogeneic hematopoietic cell transplantation (allo-HCT). Adult patients who developed HC after allo-HCT were identified from the HCT database of the Asan Medical Center and their medical records were reviewed. From December 1993 to August 2001, a total of 210 adult patients underwent allo-HCT. Fifty-one patients developed HC with a cumulative incidence of 25.7%. The median onset of HC was post-transplant day 24 (range, -2 to 474), and the median duration was 31 days (range, 8 to 369). Significant risk factors for HC by univariate analysis included diagnosis of chronic myelogenous leukemia (p=0.028), unrelated HCT (p=0.029), grade III-IV acute graft-versus-host disease (GVHD) (p<0.001), extensive chronic GVHD (p=0.001), and positive cytomegalovirus antigenemia between post transplant days 31 and 60 (p=0.031). Multivariate analysis showed that grade III-IV acute GVHD was the most important risk factor for the occurrence of HC after allo-HCT (odds ratio, 3.38; 95% CI, 1.36-8.39). Late-onset HC, which occurred beyond 3 weeks after allo-HCT, was more frequently associated with GVHD than early-onset HC (p=0.007). Our data suggest that a portion of late-onset HC might be a manifestation of GVHD.

Key Words : *Cytomegalovirus Cystitis; Hematopoietic Stem Cell Transplantation; Graft vs Host Disease*

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INTRODUCTION

Hemorrhagic cystitis (HC) is an important cause of morbidity following hematopoietic cell transplantation (HCT). The incidence of HC after HCT has been reported to range from 7% to 76% (1-5). It has varied according to the definition of hemorrhagic cystitis, conditioning regimens, type of HCT, and regimen of graft-versus-host disease (GVHD) prophylaxis. Most cases of HC occurring after HCT are self-limited, but they can cause pain, debilitation, and prolonged hospitalization. Occasionally life-threatening hemorrhage is encountered. The diagnosis of HC is usually made on clinical grounds when hematuria occurs in the absence of urinary tract bacterial infection or other causes of hematuria. Hyperhydration and chemoprotectant 2-mercaptoethane sodium sulfonate (mesna) have been commonly used to prevent HC after HCT (5, 6)

HC can occur at any time following HCT. HC in the early post-transplant period is usually associated with thrombocytopenia, busulfan (1, 7), or cyclophosphamide (5, 6). Pathogenesis of delayed presentation of hemorrhagic cystitis, occurring weeks to months post-transplant, is less clearly understood, but viruses such as BK virus (4, 8-11), adenovirus 11 (3, 12), or cytomegalovirus (CMV) (13, 14) and GVHD (15-17) have been found to be risk factors. In allogeneic HCT setting, the role of GVHD in HC is a subject of debate. HC may occur from direct viral injury or as a result of the bladder epithelium acting as a target organ for GVHD.

We conducted a retrospective study to investigate the incidence, risk factors, and clinical features of HC following allogeneic HCT.

MATERIALS AND METHODS

Patients

All adult patients who underwent allogeneic HCT in the Asan Medical Center from December 1993 to August 2001 were included in the study. We identified patients with evidence of hematuria following allogeneic HCT from the HCT database of the Asan Medical Center, reviewed their medical records and collected the clinical data relevant to hematuria.

HCT procedure

The following conditioning regimens were used: BuCy (busulfan 4 mg/kg/d for 4 days and cyclophosphamide 60

mg/kg/d for 2 days) for leukemia/MDS, Cy-ATG (cyclophosphamide 50 mg/kg/d for 4 days and antithymocyte globulin 30 mg/kg/d for 3 days) for severe aplastic anemia, and Bu-Fludara-ATG (busulfan 4 mg/kg/d for 2 days, fludarabine 30 mg/m^2/d for 6 days, and antithymocyte globulin 10 mg/kg/d for 4 days) or FM (fludarabine 30 mg/m^2/day for 5 days and melphalan 100 mg/m^2/day for 1 day) for non-myeloablative conditioning. For patients who received cyclophosphamide as a part of conditioning regimen, hyperhydration and mesna were given. Four doses of mesna 12 mg/kg were administered intravenously on each day of cyclophosphamide administration. All blood products were leukocyte-depleted by filtration and irradiated prior to transfusion. Intravenous immunoglobulin 500 mg/kg was administered at day -7, then every other week until day 120, and monthly until day 180. All patients received cyclosporine with or without methotrexate for the prophylaxis of GVHD. For the prevention of veno-occlusive disease (VOD), heparin was administered to those patients who received BuCy regimen at a rate of 100 units/kg/day from day -7 to day 30. Heparin was discontinued if there was clinically significant bleeding or the PTT exceeded 1.2 times the upper limit of control. Bone marrow (day 0) or G-CSF mobilized peripheral blood stem cells (days 0 and 1) from the donors were infused over 3-4 hr. Recombinant human granulocyte-colony stimulating factor (rhG-CSF) 300 or 450 μg was given intravenously once daily starting on day 0 or day 5.

Definition of Hemorrhagic Cystitis

HC was defined as the presence of sustained microscopic or macroscopic hematuria for 7 days or more from the beginning of conditioning therapy in the absence of other clinical conditions such as menstruation, bleeding due to other gynecologic problem, disseminated intravascular coagulation, multiple organ dysfunction syndrome or sepsis. HC was clinically graded as follows: grade 1, microscopic hematura; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with small blood clots; grade 4, massive macroscopic hematuria requiring instrumentation for clot evacuation and/or causing urinary retention. HC was classified into early (cases occurring within post-transplant day 21) or late (cases occurring after post transplant day 21) onset.

Statistical analysis

Cumulative incidence of HC from the initiation of conditioning therapy was calculated using the Kaplan-Meier method, censoring at last follow-up, death, relapse, graft failure, or performance of donor lymphocyte infusion. Clinical risk factors were analyzed for their effect on the occurrence of hemorrhagic cystitis. Differences between groups were compared by log-rank test. Variables with p-value less than 0.05 by univariate analysis were considered for entry into Cox proportional hazard model.

Differences in categorical variables between patients with early-onset HC and those with late-onset HC were tested using the chi-square test, whereas continuous variables were compared using the Mann-Whitney U test.

RESULTS

Patient characteristics

From December 1993 to August 2001, a total of 210 patients, 107 males and 93 females, underwent allogeneic HCT in the Asan Medical Center. The median age of the patients was 32 yr (range, 15 to 59). The indications for HCT were acute myelogenous leukemia in 65 patients, acute lymphoblastic leukemia in 32, acute mixed leukemia in 5, chronic myelogenous leukemia (CML) in 40, myelodysplastic syndrome in 12, aplastic anemia in 27, non-Hodgkin's lymphoma in 9, paroxysmal nocturnal hemoglobinuria in 5, solid tumor in 9, and miscellaneous in 6. Stem cell donors were siblings in 166 patients and unrelated volunteers in 44. Stem cell grafts were bone marrow in 179 patients and G-CSF mobilized peripheral blood in 31. Conditioning regimens were BuCy in 150 patients, BuCy plus cytarabine or etoposide in 3, Cy-ATG in 27, Bu-Fludara-ATG in 28, and FM in 2. For the prophylaxis of GVHD, 162 patients received cyclosporine plus methotrexate and 48 received cyclosporine only.

Clinical features of HC

Of the 210 patients in the study, 51 developed HC with a cumulative incidence of 25.7%. The median onset of HC was post-transplant day 24 (range, day -2 to 474). In 24 patients, the onset of HC was within post-transplant day 21 (early onset) and in 27, the onset was later than post-transplant day 21 (late onset). The median duration of HC was 31 days (range, 8 to 369 days). Clinical grade of HC was as follows: grade I in 19 patients, grade II in 19, grade III in 9, and grade IV in 4. The symptoms and signs of HC were urinary frequency in 27 patients (53%), tenesmus in 23 (45%), dysuria in 11 (22%), urgency in 6 (12%), azotemia in 5 (10%), and urinary obstruction in 3 (6%). Fourteen patients (28%) required bladder catheterization with irrigation and 3 (6%) intravesical instillation of alum. One patient with grade IV HC died of uncontrolled bleeding due to severe hemorrhagic cystitis. In another patient with grade IV, HC developed on post transplant day 35, and lasted for 369 days with intermittent urinary obstruction and azotemia. Although HC resolved eventually, severe urinary stricture was found on day 457 by retrograde urethrography and urethral dilatation was performed on day 461. In the remaining 2 patients with grade IV HC, HC persisted until they died of disease progression and GVHD, respectively.

Table 1. Cumulative incidence of hemorrhagic cystitis according to clinical characteristics

Characteristics	No. of patients	Cumulative incidence of hemorrhagic cystitis	*p*-value
Sex			
Male	117	26.7%	0.895
Female	93	24.6%	
Age			
30 yr or less	99	23.7%	0.408
Over 30 yr	111	27.3%	
Diagnosis of underlying disease			
Acute leukemia/MDS	114	19.6%	0.028
CML	40	42.0%	
Others	56	26.7%	
Time from diagnosis to HCT			
130 days or less	102	20.3%	0.110
Over 130 days	108	31.1%	
Disease status at HCT			
Standard risk	140	22.0%	0.080
High risk	70	33.3%	
Conditioning regimen			
BuCy based regimen	153	27.3%	0.228
Cy-ATG	27	27.5%	
Non-myeloablative	30	13.0%	
Stem cell donor			
Sibling	166	21.8%	0.029
Unrelated	44	41.9%	
Source of stem cells			
Bone marrow	179	27.8%	0.072
Peripheral blood	31	12.1%	
GVHD prophylaxis			
Cyclosporine only	48	26.5%	0.715
Cyclosporine plus methotrexate	162	23.1%	
VOD prophylaxis			
No use of heparin	61	20.5%	0.135
Use of heparin	149	28.0%	
Acute GVHD, grade III-IV			
No	170	17.7%	<0.001
Yes	29	73.1%	
Chronic GVHD, extensive			
No	120	15.8%	0.001
Yes	50	41.6%	
CMV infection within day 30			
No	203	24.9%	0.156
Yes	7	50.0%	
CMV infection, day 30 to 60			
No	176	20.4%	0.031
Yes	34	38.2%	
Hepatic VOD			
No	131	27.9%	0.718
Yes	79	22.2%	

MDS; myelodysplatic syndrome, CML; chronic myelogenous leukemia, GVDH; graft-versus-host disease, CMV; cytomegalovirus, VOD; veno-occlusive disease.

Risk factors for hemorrhagic cystitis

Table 1 illustrates cumulative incidence of HC according to clinical characteristics. Significant risk factors for HC by univariate analysis included diagnosis of CML (p=0.028), unrelated donor HCT (p=0.029), acute GVHD of grade III to IV (p<0.001), extensive chronic GVHD (p=0.001), and positive CMV antigenemia between post-transplant day 31 and 60 (p=0.031). These risk factors were entered into Cox proportional hazard model (Table 2). Multivariate analysis showed that grade III to IV acute GVHD was the most important risk factor for the occurrence of HC after allogeneic HCT (odds ratio, 3.38; 95% confidence interval, 1.36-8.39; Fig. 1).

Table 2. Multivariate analysis of risk factors for hemorrhagic cystitis

Variable	Odds ratio	95% confidence interval	*p*-value
Diagnosis			
Acute leukemia/MDS	1.000		
CML	1.624	0.686-3.844	0.270
Others	0.716	0.275-1.862	0.493
Stem cell donor			
Sibling	1.000		
Unrelated	1.698	0.731-3.943	0.476
Acute GVHD, grade III-IV			
No	1.000		
Yes	3.376	1.358-8.390	0.009
Chronic GVHD, extensive			
No	1.000		
Yes	1.698	0.731-3.943	0.218
CMV infection, day 30 to 60			
No	1.000		
Yes	1.594	0.651-3.901	0.307

GVDH; graft-versus-host disease, CMV; cytomegalovirus.

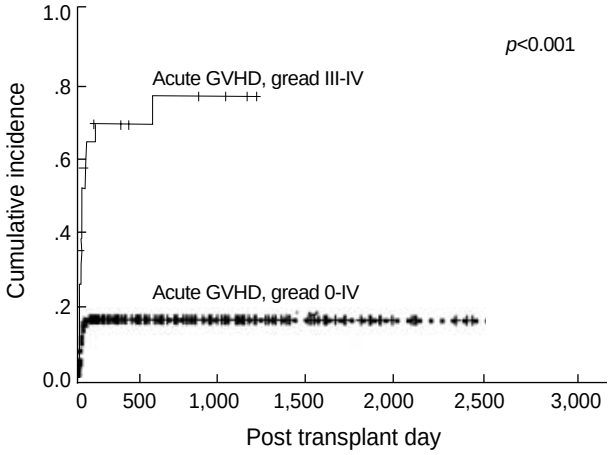

Fig. 1. Cumulative incidence of hemorrhagic cystitis according to the occurrence of grade III-IV acute GVHD.

Early-onset vs late-onset hemorrhagic cystitis

Among 51 patients with hemorrhagic cystitis, 25 (49%) had

Table 3. Early-onset vs late-onset hemorrhagic cystitis

Characteristics	Early onset (within day 21)	Late onset (after day 21)	*p*-value
Number of patients	25 (49%)	26 (51%)	
Grade of hemorrhagic cystitis			
Grade I	11 (44%)	8 (31%)	0.564*
Grade II	8 (32%)	11 (42%)	
Grade III	6 (24%)	4 (15%)	
Grade IV	0 (0%)	3 (12%)	
Onset of hemorrhagic cystitis			
Median (range)	day 10 (-2 to 21)	day 38 (24 to 474)	
Duration of hemorrhagic cystitis, day			
Median (range)	40 (9 to 135)	30 (8 to 369)	0.970†
Platelet count at onset, $x10^3/\mu L$			
Median (range)	24 (7 to 290)	30 (6 to 279)	0.336†
PT at onset, INR			
Median (range)	1.14 (0.91 to 2.44)	1.13 (0.93 to 1.52)	0.713†
PTT at onset, second			
Median (range)	44.8 (35.2 to 76.9)	51.0 (28.8 to 110.9)	0.157†
GVHD at onset			
No	22 (88%)	14 (54%)	0.007*
Yes	3 (12%)	12 (46%)	
CMV infection at onset			
No	24 (96%)	22 (85%)	0.172*
Yes	1 (4%)	4 (15%)	
CMV viruria at onset			
No	1 (50%)	5 (63%)	0.747*
Yes	1 (50%)	3 (37%)	

*chi-square test; †Mann-Whitney U test.
PT; prothrombin time, PTT; activated partial thromboplastin time, GVDH; graft-versus-host disease, CMV; cytomegalovirus, INR; international normalized ratio.

early-onset HC (until post transplant day 21) and 26 (51%) had late-onset HC (after post-transplant day 21) (Table 3). Clinical grade and duration of HC were not significantly different between the two groups. Platelet count and coagulation times at the onset of HC were also similar between the two groups. A higher proportion of patients with late-onset HC had GVHD at the onset of HC than those with early-onset HC (p=0.007).

DISCUSSION

HC following HCT is multifactorial in origin and the potential causes included chemical toxins, radiation, viruses, immunologic mechanism, and idiopathic etiologies (5, 6). Cyclophosphamide, which is used frequently as a part of most conditioning regimens, is a well-defined etiology of hemorrhagic cystitis. Acrolein, a urinary metabolite of cyclophosphamide, is thought to be responsible for the urothelial toxicity (18). Although hyperhydration and use of mesna have decreased the incidence of hemorrhagic cystitis, cyclophosphamide may still be a major cause of early-onset HC after HCT. Urinary excretion of viruses such as BK virus (4, 8-11), adenovirus 11 (3, 12), or CMV (13, 14) has been reported to be strongly associated with HC after HCT. The virus most frequently implicated is the BK virus. Arthur et al. (8) suggested that reactivation of BK virus might account for a substantial proportion of late-onset, long-lasting HC in HCT recipients. Bedi et al. (4) showed that HC occurred in half of the patients with persistent BK viruria and in none of the patients without excretion of BK virus. Leung et al. (9) demonstrated that BK viruria was quantitatively related to the occurrence of HC after HCT. They also observed that BK viruria was detected in 2 of 5 patients with pre-engraftment HC and in 21 of 27 patients with post-engraftment hemorrhagic cystitis (17). They suggested that BK virus might be involved in the pathogenesis of both early and late onset hemorrhagic cystitis. We did not examine urinary excretion of BK virus or adenovirus. Five of 10 patients, in whom urine CMV cultures were performed at the onset of hemorrhagic cystitis, had CMV viruria.

The role of GVHD in the pathogenesis of HC remains unclear. HC may occur as a result of uroepithelium acting as a target organ for GVHD rather than from direct viral injury, while the immunosuppressive state associated with GVHD may also increase the reactivation of virus. Arthur et al. (8) observed a higher incidence of HC in the recipients of allogeneic HCT compared to those of autologous HCT. GVHD has been reported to be a risk factor for HC after allogeneic HCT in several studies. Ost et al. (15) observed that 20 of

125 recipients of allogeneic HCT developed late-onset HC and there was a correlation between the severity of HC and severity of acute GVHD. They suggested that bladder epithelium might be a target for GVHD, although the typical mononuclear inflammatory infiltrates were not seen on biopsy or at autopsy. Ruutu et al. (19) also argued that severe late-onset HC might in itself be a manifestation of chronic GVHD. Leung et al. (17) suggested that attack of urothelium by immune cells, possibly directed against BK viral antigens, might play a pathogenetic role. However, Sencer et al. (3) did not find GVHD to be significantly associated with HC in their large series. Bedi et al. (4) failed to show that the frequency of HC was related to occurrence of acute or chronic GVHD. We investigated the risk factors for HC in the patients who underwent allogeneic HCT. Acute GVHD of grade III to IV was the only independent risk factor for HC by multivariate analysis. Late-onset hemorrhagic cystitis, which was defined as HC occurring beyond 3 weeks after HCT, were more frequently associated with GVHD than early-onset hemorrhagic cystitis. Our data suggest that a portion of late-onset HC might be a manifestation of GVHD.

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