Viruria in Adult Hemorrhagic Cystitis Patients Following Allogeneic Hematopoietic Stem Cell Transplantation and Implication of Antiviral Treatment

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Background: Viruria is frequently detected in patients who have had hemorrhagic cystitis (HC) following allogeneic hematopoietic stem cell transplantation (allo-HSCT). Urinary viruses, especially BK virus, have been suggested as a cause of HC following allo-HSCT, therefore antiviral therapy is emerging as a therapeutic approach for its treatment.

Methods: Adult HC patients who underwent allo-HSCT from January 2005 to March 2006 at a single institution were enrolled. We performed a PCR-based assay for BK virus, JC virus, and CMV virus in urine obtained from the patients to determine the incidence of viruria, and the type of virus detected in the urine, and the effect of treatment with cidofovir on HC.

Results: Of 155 patients that received allo-HSCT during the study period, 22 (14.2%) experienced HC. A viral study of urine obtained from 19 of these 22 patients revealed that 16 (84.2%) had viruria. Eleven patients had grade III-IV HC, 5 of which were treated with intravenous cidofovir. Three of the HC patients who underwent treatment responded to cidofovir, 1 had no response, and 1 had a complete response followed by recurrence.

Conclusion: Most adult HC patients (84.2%) had viruria following allo-HSCT, however the response rate to antiviral therapy with intravenous cidofovir for the treatment of high grade HC (grade III-IV) was 80%. Therefore, antiviral therapy should be considered if high grade HC does not respond to hyperhydration and transfusional support. ***(Korean J Hematol 2007;42:114-121.)***

Key Words: Viruria, Cystitis, Hematopoietic stem cell transplantation, and Cidofovir

INTRODUCTION

Hemorrhagic cystitis (HC) is an important cause of morbidity and occasional mortality in allogeneic hematopoietic stem cell transplantation (allo-HSCT). The incidence and severity of HC after allo-HSCT has been reported to vary according to the transplantation conditions.[1-3] HC

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is graded from I to IV according to severity.[4] Although low grade HC (grade I-II) usually subsides with platelet transfusion and intravenous hyperhydration, high grade HC (grade III-IV) may require an invasive procedure such as intravesical recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) instillation, intravesical alum irrigation, or transarterial embolization (TAE) which can induce low abdominal pain or unexpected complications.[5-7] The HC before engraftment usually results from chemotherapeutic agents like cyclophosphamide, while HC after engraftment may be associated with a virus in the urinary tract.[4,8] However, most therapeutic methods which have been used for late-onset (post-engraftment) HC are not targeted to the underlying cause. Despite of many different therapies being described, no definitive treatment has been established. Recent studies imply that the important viruses causing late-onset HC after allo-HSCT are BK virus, JC virus, adenovirus, and cytomegalovirus (CMV) virus[1,4,8-12] and antiviral therapy is emerging as an promising treatment for HC. In this study, the frequency of viruria in adult patients who developed HC after allo-HSCT and the types of virus detected in urine in those patients were analyzed. In addition, the treatment outcome of HC with

Table 1. Clinical characteristics of the adult patients who had hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation

	No. of patients (%)		No. of patients (%)
Age (median, range)	35, 18~68	*Ex-vivo*	1 (4)
Gender		Acute GVHD	
Male	15 (68)	0	8 (36)
Female	7 (32)	I	8 (36)
Diagnosis		II	4 (18)
AML	9 (40)	III	0 (0)
ALL	12 (55)	IV	2 (10)
MM	1 (5)	Chronic GVHD	
Transplantation		None	5 (23)
sBMT	3 (14)	Limited	6 (27)
sPB+BMT	3 (14)	Extensive	1 (5)
sPBSCT	4 (18)	N/E	12 (55)
HaploidPBSCT	1 (4)	Survival	
uBMT	6 (27)	Alive	10 (45)
uPBSCT	3 (14)	Dead	12 (55)
uCBT	2 (9)	Cause of death	
Conditioning		Renal failure-associated	4 (33)
TBI-based	17 (77)	Infection	2 (17)
Fludarabine-based	5 (23)	Leukemic relapse	3 (25)
T-cell depletion		GVHD	2 (17)
None	16 (73)	CNS infarct	1 (8)
*In-vivo**	5 (23)		

*The case that alemtuzumab was used in conditioning period is defined as *in-vivo* T cell depletion.
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MM, multiple myeloma; sBMT, sibling donor bone marrow transplantation; sPB+BMT, transplantation using peripheral blood stem cell plus bone marrow stem cell from sibling donor; sPBSCT, sibling donor peripheral blood stem cell transplantation; uBMT, unrelated donor bone marrow transplantation; uPBSCT, unrelated donor peripheral blood stem cell transplantation; uCBT, unrelated donor cord blood transplantation; HaploidPBSCT, haploidentical peripheral blood stem cell transplantation; TBI, total body irradiation; N/E, not evaluable; CNS, central nervous system; HC-associated; hemorrhagic cystitis-associated.

cidofovir, an antiviral agent, was assessed.

MATERIALS AND METHODS

1. Patients

A total of 155 patients underwent allo-HSCT in Catholic Hematopoietic Stem Cell Transplantation Center, the Catholic University of Korea from January 2005 to March 2006. All transplant patients who had cyclophosphamide as the conditionings received prophylaxis for chemical HC with 2-mercaptoethane sulphonate (MESNA). Among the 155 patients, 22 (14.2%) patients developed HC after transplant; 3 experienced HC before day 21 post-transplant, 14 after day 21 post-transplant, and 5 before and after day 21 post-transplant continuously. The characteristics of HC patients are listed in Table 1. Of the patients who had high grade HC, 5 were treated with cidofovir.

2. Definition and grading of hemorrhagic cystitis

HC was defined as the presence of sustained hematuria over 24 hours anytime after the beginning of conditioning therapy in the absence of vaginal bleeding, generalized bleeding diathesis, and bacterial or fungal urinary tract infection. Clinical grading of HC was defined as I to IV according to the severity (Table 2).

3. Viral study of the urine of the hemorrhagic cystitis patients

To identify the presence of viruria and types of virus, polymerase chain reaction (PCR)-based assays for the DNA of CMV, BK virus, and JC virus were performed with the urine of the 19 patients at the time of defining the HC among the 22 HC patients. PCR for the DNA of BK virus and JC virus was conducted according to the method of Fedele et al.[13] The products (353 bp for BKV and 189 bp for JCV) were analyzed by electrophoresis. For identification of CMV, the method of Yamamoto et al. with the external primers MIE-4 and MIE-5 and the internal primers IE-1 and IE was used.[14]

Table 2. Clinical grading of hemorrhagic cystitis

Grade	Severity
I	Microscopic hematuria
II	Macroscopic hematuria
III	II+presence of blood clot
IV	III+renal impairment due to urinary obstruction

4. Treatment for hemorrhagic cystitis

All HC patients received intravenous hyperhydration (IVH) with normal saline and received transfusional support to maintain the platelet count above 50×10^9/L. If the grade of HC was III or IV, continuous bladder irrigation with water (CBIW) was performed. If the high grade HC did not respond to CBIW, additional (third-line) therapeutic methods such as, intravesical rhGM-CSF instillation, intravesical alum irrigation, TAE, and intravenous cidofovir infusion were considered.

5. Criteria for response to treatment

Complete response (CR): hematuria and symptoms ceased after treatment. Partial response (PR): the grade of HC was diminished but hematuria is persistent. No response (NR): no decrease of the grade of HC despite treatment. Recurrence: start of hematuria over one week after achieving a CR.

RESULTS

1. Patient characteristics

Patient characteristics are listed in Table 1. A total of 22 HC patients, 15 males and 7 females, were analyzed. The median age of the patients was 35 years (range, 18 to 68). The diagnoses of the patients were acute lymphoblastic leukemia (n=12), acute myeloid leukemia (n=9), and mul-

Table 3. Profound immunosuppression state and clinical courses of hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation

No. case	Steroid pulse Tx	T-cell depletion	Grade	Virus study	Treatment	Outcome	HC-associated death*
1	No	No	1	N/E	IVH	CR	No
2	Yes	No	2	BK	IVH	CR	No
3	No	Yes (*in-vivo*)	2	BK	IVHCR	No	
4	Yes	No	3	Negative	IVH	CR & relapse	No
5	No	No	1	N/E	IVH	CR	No
6	Yes	No	4	JC	IVH, CBI, CDV	CR	No
7	Yes	No	4	BK/CMV	IVH, CBI, GMCSF	NR	Yes
8	No	Yes (*ex-vivo*)	4	BK	IVH, CBI, GMCSF, AI, CDV	NR	Yes
9	Yes	No	4	JC	IVH, CBI, TAE	NR	Yes
10	No	No	1	N/E	IVH	CR	No
11	Yes	No	3	BK	IVH, CBI, CDV	CR	No
12	Yes	No	3	BK	IVH, CBI, CDV	CR	No
13	No	No	2	Negative	IVH	CR	No
14	No	Yes (*in-vivo*)	3	BK	IVH	CR	No
15	Yes	No	2	BK	IVH	CR	No
16	No	No	2	BK	IVH	CR	No
17	No	Yes (*in-vivo*)	4	JC	IVH, CBI	NR	Yes
18	Yes	Yes (*in-vivo*)	2	BK	IVH	CR	No
19	Yes	No	2	Negative	IVH	NR	No
20	Yes	No	3	JC	IVH, CBI	CR	No
21	Yes	No	2	JC/BK	IVH	CR	No
22	Yes	Yes (*in-vivo*)	4	BK	IVH, CBI ,CDV	CR & relapse	No

Abbreviations: N/E, not evaluable; BK, BK virus; JC, JC virus; CMV, cytomegalovirus; IVH, intravenous hyperhydration; CBI, continuous bladder irrigation with water; CDV, intravenous cidofovir; GMCSF, intravesical recombinant human granulocyte-macrophage colony-stimulating factor instillation; AI, intravesical alum irrigation; TAE, transarterial embolization; CR, complete response; NR, no response.

tiple myeloma (n=1). The donor types were a HLA-matched sibling donor for 10 patients, a HLA-matched/mismatched unrelated donor for 11 patients, and a haploidentical familial donor for 1 patient. The stem cell source was bone marrow for 9 patients, peripheral blood for 8 patients, bone marrow plus peripheral blood for 3 patients, and cord blood for 2 patients. The intensities of conditioning regimens were standard in 17 patients and reduced in 5 patients. *In-vivo* T cells depletion with alemtuzumab in 5 patients and ex-vivo T cells depletion in one patient who underwent haploidentical transplantation were conducted.

2. Virus study of HC

Nineteen HC patients were tested for viruria. The test results and clinical courses of the patients are presented in Table 3. Only one out of 3 patients who had HC only before day 21 post-transplant was tested for viruria and the result was negative. Among the nineteen patients who had HC either before and after day 21 post-transplant continuously or after 21 day post-transplant, 18 patients were evaluated for viruria. Sixteen patients (84%) out of the 19 evaluable patients had viruria. All patients who had HC before and after day 21 post-transplant continuously had viruria. The most frequent virus de-

tected was BK virus (n=12) followed by JC virus (n=5) and CMV (n=1). Two patients had two types of virus simultaneously in their urine.

3. Clinical features and treatment of HC

The median onset of HC was day 46 post-transplant (range, 0 to 244) and the median duration of HC was 30 days (range, 3 to 112). In 8 patients (36%), the onset of HC was before day 21 post-transplant. Four of the 8 early-onset HC patients suffered from long-lasting HC even after engraftment. In 14 patients (64%), the onset of HC was after day 21 post-transplant. Eleven patients (50%) had grade I or II HC and eleven patients (50%) had grade III or IV HC. The treatment outcome of HC in this study group is depicted in Fig. 1. Out of the patients who had grade I-II HC, 10 (91%) completely resolved with IVH, while one patient (9%) died of acute GVHD without any change of HC. Out of the 11 patients who had grade III or IV, one had CR with IVH, one relapsed after CR, and the remaining 9 had NR. The 9 patients with NR to IVH received continuous bladder irrigation with water (CBIW); one

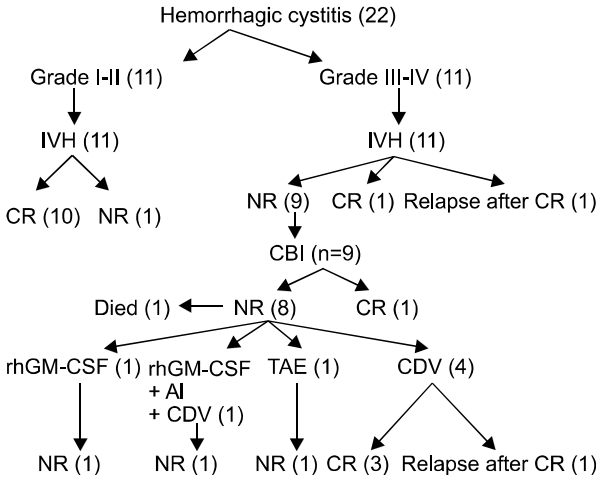

Fig. 1. Treatment outcome of hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. Abbreviations: IVH, intravenous hyperhydration ; CR, complete response; NR, no response; CBI, continuous bladder irrigation with water; rhGM-CSF, intravesical recombinant human granulocyte-macrophage colony-stimulating factor instillation; AI, intravesical alum irrigation; CDV, intravenous cidofovir; TAE, transarterial embolization.

showed CR and the others (n=8) did not respond. Among the 8 unresponders to CBIW, 7 patients received alternative third-line treatment; intravesical rhGM-CSF instillation (n=2), intravesical alum irrigation (n=1), TAE (n=1), and intravenous cidofovir (n=5). No additional treatment except intravenous cidofovir was effective in this group of patients. Out of 11 patients with grade III-IV HC, 4 (36%) died of HC associated complications.

4. Hemorrhagic cystitis and profound immunosuppressive state

All 11 patients who had grade III-IV HC received either steroid pulse therapy for the GVHD (n=7) or T cell depletion for the prophylaxis of GVHD (n=3) before the time of HC or both (n=1) (Table 3). Among the patients who underwent T-cell depleted transplantation in this study group (n=5), 4 (80%) did not have GVHD but experienced HC. Among the 19 patients who experienced HC after day 21 post-transplant, steroid pulse therapy or T cell depletion (*in vivo* or *ex vivo*) was conducted because of treatment or prophylaxis of GVHD before or during the time of HC in 17 patients (90%). These two analyses imply that profound immunosuppression may be a risk factor of post-engraftment HC and associated with the severity.

5. Dose of antiviral agent and treatment outcome

Among the 8 unresponders to CBIW who had grade III-IV HC, 5 patients received intravenous cidofovir. The intravenous dose of cidofovir was 5 mg/kg once weekly for two weeks, followed by 5 mg/kg once every other week until the HC grade decreased to grade I. The amount of infused cidofovir was 4 doses in one patient, and 2 doses in four patients. One patient among 5 patients died of HC-associated renal failure and pneumonia without improvement of HC. Another one patient relapsed after CR. He died of leukemic relapse, regardless of HC. The remaining

three (60%) patients are still alive without hematuria. There was no significant cidofovir related toxicities including nephrotoxicity and hematologic side effect.

DISCUSSION

This study found that the incidence of viruria of HC after allo-HSCT was 84% and the types of virus detected in the urine of the patients were BK virus (75%), JC virus (26%), and CMV virus (5%). The response rate of cidofovir for grade III-IV HC was 80% including a patient who relapsed after CR, while the use of other alternative therapeutic methods such as TAE, intravesical rhGM-CSF, and intravesical alum instillation did not show any response.

The pathogenesis leading to HC has not been elucidated. Viral infection in the urinary tract due to immunosuppression and alloimmune reactions may be contributory for this complication, especially for late-onset (post-engraftment) HC. Viruses which have been reported as the cause of HC after HSCT are BK virus, JC virus, adenovirus, CMV, herpes simplex virus, and influenza A virus.[8-12,15] The incidences of each type of virus in urine in this study are similar to that described in a prior report.[1] BK virus was the most common virus detected in HC after HSCT. However, the exact pathogenetic link between BK virus and HC remains unclear because reactivation of the BK virus during allo-HSCT is common even in the patients without HC after allo-HSCT.[1] One piece of evidence for this relation is that BK viruria is quantitatively related to the occurrence of HC after bone marrow transplantation.[16] We performed only a qualitative test and did not check for quantitative viruria, but antiviral therapy showed effectiveness in 80% of patients who did not respond even to CBIW which suggests that virus in the urinary tract is strongly linked with HC after allo-HSCT.

A prior report has indicated that GVHD and HC after allo-HSCT are closely associated, but the report did not analyze the relation between the incidence or grade of HC and the profound immunosuppressive state of the patients when the patients are under steroid pulse therapy or have received T cell depletion transplantation.[17] Among these study subjects, most patients who received T cell depletion transplantation did not have GVHD before the onset of HC, but they experienced HC. This study also showed that all patients with grade III-IV HC received T-cell depletion transplants or undertook steroid pulse therapy before or during the time of HC, which suggests that profound immunosuppression for the treatment or prophylaxis for GVHD can induce or aggravate HC. However, there is a limitation with this conclusion because the number of patients in this study group was small and no comparison was made with non-HC patients.

The HC related mortality of the patients with high grade HC is high (36%) as shown in this study. However, the treatment of late-onset (post-engraftment) HC has not been established despite many different therapies being described such as TAE, intravesical rhGM-CSF, intravesical alum instillation, epidermal growth factor, and estrogen.[6,7,18,19] In this study, all third-line therapeutic approaches but intravenous cidofovir infusion did not showed any response. Cidofovir, a cytosine nucleoside analog, has a broad antiviral spectrum against the viruses which can be encountered in HC after HSCT including polyoma virus, adenovirus, and CMV.[20,21] Prior reports have indicated that treatment with cidofovir was feasible without significant complications.[15,22] Although the number of patients with high grade HC undergoing each third-line therapeutic method was so small that a comparison of outcome of each method is difficult in this study, our treatment outcome also suggests intravenous cidofovir is more effective than other therapeutic approaches and shows a high response rate without any significant complication. However, in most case of grade I-II HC, hyperhydration and transfusional support acquired

CR, which suggests this expensive antiviral agent should be spared for high grade HC.

This study revealed that 1) most adult patients with HC had viruria at the time of HC, 2) profound immunosuppressive state might be related to the severity of HC and 3) antiviral therapy was effective in grade III-IV HC, which support the fact that the reactivation of virus in the urinary tract is a main pathogenesis of HC and antiviral therapy is the important treatment modality for late-onset HC after allo-HSCT. Therefore, if high grade HC does not respond to hyperhydration and transfusional support, a reduction of the immunosuppressant when GVHD is tolerable and the addition of antiviral therapy should be considered.

요 약

배경: 동종조혈모세포이식 후 출혈성 방광염 환자에서 흔히 바이러스뇨증이 발견된다. 요로계 바이러스, 특히 BK 바이러스가 동종조혈모세포이식 후 발생하는 출혈성 방광염의 중요한 원인으로 제시되고 있고 항바이러스 약제가 치료의 중요한 요소가 되고 있다.

방법: 2005년 1월부터 2006년 3월까지 단일기관에서 동종조혈모세포이식을 시행한 환자 중 출혈성 방광염이 생긴 환자의 소변에서 검사한 BK 바이러스, JC 바이러스, CMV 바이러스에 대해 시행한 PCR 결과를 확인하고, 치료방법과 치료 성적을 분석하였다.

결과: 연구기간 동안 155명의 환자가 동종조혈모세포이식을 받았고, 이 중 22명(14.2%)의 환자가 출혈성 방광염을 경험하였다. 22명 중 19명이 바이러스 검사를 받았고, 이 중 16명(84.2%)의 환자가 바이러스뇨증이 있음을 확인하였다. 가장 흔하게 검출된 바이러스는 BK 바이러스(12명)이고, JC 바이러스(5명)와 CMV (1명) 순이었다. 두 명의 환자에서는 두 종류의 바이러스가 검출되었다. 3등급이상의 출혈성 방광염을 가진 11명의 환자 중에서 5명이 정맥을 통한 cidofovir를 투여 받았고, 3명이 완전반응, 1명이 반응 후 재발을 보였으며, 나머지 1명은 반응을 보이지 않았다.

결론: 성인 동종조혈모세포이식 후 발생하는 출혈성 방광염은 대부분(84.2%) 바이러스뇨증을 보이며, 3등급 이상의 출혈성 방광염에 대한 cidofovir 정맥투여는 80%의 반응을 보였다. 따라서 3등급 이상의 출혈성 방광염이 충분한 수액 투여와 수혈에 반응이 없다면 항바이러스 치료를 고려해야 할 것이다.

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