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# BK virus-associated hemorrhagic cystitis after pediatric stem cell transplantation

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Hemorrhagic cystitis is a common stem cell transplantation-related complication. The incidence of early-onset hemorrhagic cystitis, which is related to the pretransplant conditioning regimen, has decreased with the concomitant use of mesna and hyperhydration. However, late-onset hemorrhagic cystitis, which is usually caused by the BK virus, continues to develop. Although the BK virus is the most common pathogenic microorganism of poststem cell transplantation late-onset hemorrhagic cystitis, pediatricians outside the hemato-oncology and nephrology specialties tend to be unfamiliar with hemorrhagic cystitis and the BK virus. Moreover, no standard guidelines for the early diagnosis and treatment of BK virus-associated hemorrhagic cystitis after stem cell transplantation have been established. Here, we briefly introduce poststem cell transplantation BK virus-associated hemorrhagic cystitis.

**Key words:** Cystitis, Stem cell transplantation, BK virus, Child

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Received: 16 September, 2014

Accepted: 8 October, 2014

## Introduction

Hemorrhagic cystitis (HC) occurs in 9%–31% of all stem cell transplantation (SCT) recipients<sup>1-6</sup>. This complication is associated with increased morbidity and mortality, and particularly with urinary tract obstruction, renal dysfunction and renal failure, longer hospital stay, and increased hospital costs<sup>2,6-10</sup>. In the early period after SCT, chemotherapeutic agents such as cyclophosphamide and busulphan as well as irradiation administered during the pretransplant conditioning period can directly damage the bladder urothelium<sup>11-15</sup>. However, several complicating factors such as viral infection and acute graft-versus-host disease (GvHD) may cause HC in the late period following SCT<sup>3,11,14</sup>. In particular, a relationship between BK virus (BKV) infection and late-onset HC after SCT has been described<sup>1,3,16-19</sup>. Few reports have examined the impact of BKV infection on HC after SCT in Korea, where pediatric SCT has been performed since 1983<sup>20,21</sup>.

This review will introduce the pathogenesis, clinical features, diagnosis, and treatment of BKV-associated HC after SCT.

## Definition and grading of HC

HC is defined as the development of microscopic or gross hematuria accompanied by lower urinary tract symptoms such as dysuria, frequent urination, urgency, and suprapubic pain. Other causes of bleeding such as bleeding tendency, bacterial or fungal infection, urinary tract mass, and vaginal bleeding should be excluded<sup>14,22</sup>. HC is categorized into

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**Table 1.** Grades of hemorrhagic cystitis

Grade	Manifestations
I	Microscopic hematuria
II	Macroscopic hematuria
III	Macroscopic hematuria with blood clots
IV	Renal impairment due to urinary tract obstruction

four grades based on the severity of hematuria and its effect on the upper urinary tract (Table 1)<sup>14</sup>.

## Causes of HC in SCT

While a variety of time frames ranging from 48 hours to two weeks have been proposed<sup>1,12,19,23,24</sup>, post-SCT HC is generally divided into early-onset or pre-engraftment HC and late-onset or postengraftment HC. Early-onset HC is caused by chemotherapeutic agents including cyclophosphamide, ifosfamide, busulphan, and etoposide. It can also be caused by the irradiation administered to the pelvic area during the pretransplant conditioning period and by sustained thrombocytopenia prior to engraftment<sup>11,12,14,25</sup>. Sustained thrombocytopenia and coagulopathy may also cause HC in the late period after SCT. However, infections with viruses such as BKV, JC virus, cytomegalovirus (CMV), and adenovirus have been reported as major causes of late-onset HC after SCT<sup>1,11,17-19,23</sup>. Urinary BKV is detected in 35%–100% of SCT recipients with HC<sup>1,3,17</sup>, compared to ranges of 10%–15%<sup>9,26,27</sup>, 4%–26%<sup>9,23,27</sup>, and 4%–7%<sup>3,26</sup> for adenovirus, CMV, and JC virus, respectively. Thus, BKV is the most important pathogenic microorganism of late-onset HC after SCT.

## Pathophysiology of BKV-associated HC

BKV is a member of the Polyomaviridae family and is a nonenveloped double-stranded DNA virus. First detected in 1970 in a postkidney transplant patient suffering from nephropathy, the virus was named “BK virus” after the patient’s initials<sup>28</sup>. While BKV infects humans during childhood, a latent infection is maintained in the urinary tract<sup>16,29</sup>. Anti-BKV antibodies are present in approximately 80% of the general population and 91% of children aged 5–9 years<sup>30,31</sup>, and urinary BKV excretion is detected in 7%–14% of all immune-competent hosts<sup>30,32</sup>. Latent BKV is reactivated under immunosuppressed conditions, and BK viremia and viremia are detected in 53%–71%<sup>10,16,33</sup> and 17%–51%<sup>10,34</sup> of SCT recipients, respectively, regardless of HC status.

Late-onset HC after SCT is believed to develop in three phases<sup>14,16,33,35</sup>. The first is direct bladder mucosal damage

caused by chemotherapeutic agents and irradiation received during pretransplant conditioning. During the second phase, BKV replication is activated in conjunction with the activated regeneration of damaged urothelial cells under the immunosuppressed status immediately following SCT. The third and final phase comprises an excessive inflammatory response of the reconstituted host immunity against activated BKV.

Although BK viremia were detected in 47%–52% of all SCT recipients<sup>1,26,33</sup>, only 38%–44% of them exhibited HC<sup>1,26</sup>. Moreover, 9%–50% of SCT recipients with HC did not exhibit BK viremia<sup>2,6,26,27,33</sup>. These findings indicate that factors other than BKV reactivation may contribute to the development of late-onset HC. Old age, acute GvHD, receiving stem cells from an unrelated donor, myeloablative conditioning, and allogeneic transplantation have all been suggested as possible contributing factors<sup>1,3-5,7,9,19,23,24,36,37</sup>.

## Clinical features of BKV-associated HC

BKV infection after kidney transplantation mainly manifests as BKV-associated nephropathy while BKV infection after SCT mainly manifests as HC<sup>25,35</sup>. In various studies, BKV-associated HC was found to occur 25–57 days (median values) after SCT, with symptoms lasting for 10–38 days (median values)<sup>3,4,8,16,17,20,34,38</sup>. In terms of severity, HC of grades I, II, III, and IV occurred in 0%–30%, 16%–57%, 36%–67% and 0%–12% of cases, respectively<sup>3,4,8,20,38</sup>. Conservative care tends to be effective in patients with lower grades of HC, while those with higher grades may suffer from renal complications and even death.

## Diagnosis of BKV-associated HC

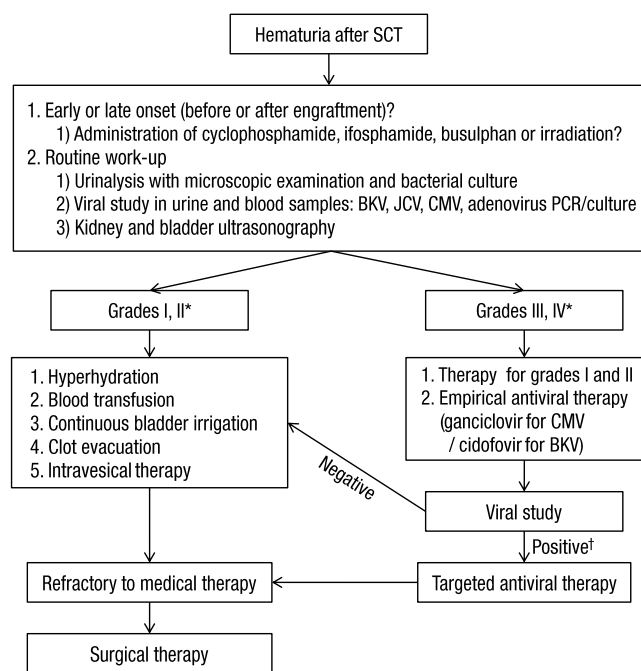
BKV-associated HC is diagnosed when an SCT recipient with grade II or higher HC complains of lower urinary tract symptoms such as dysuria, urinary frequency, urgency, and suprapubic pain and shows laboratory evidence of BKV replication<sup>39</sup>. Ultrasonography can be useful in the evaluation of blood clot formation and the severity of upper urinary tract complications<sup>22</sup>. Polymerase chain reaction (PCR)-mediated detection of BKV DNA is the modality of choice for diagnosing BK viremia<sup>11</sup>. BK viremia tend to precede clinical symptoms of HC, and therefore, PCR for urinary BKV can be useful in the early diagnosis of BKV-associated HC<sup>1,17,19,33</sup>. Previous studies reported that 10<sup>6</sup> copies/mL or 9 × 10<sup>6</sup> copies/mL of urinary BKV DNA was an amount significantly associated with the development of BKV-associated HC<sup>1,17</sup>. However, PCR for blood BKV DNA may be an even more valuable predictor of the development of BKV-associated HC since compared with BK viremia, BK viremia has been shown

to be more significantly related to the severity of HC and the development of renal complications<sup>2,6,8,10</sup>. In addition, various cutoff values of blood BKV DNA titers, including 10<sup>3</sup> and 10<sup>4</sup> copies/mL, have been reported to predict the development of BKV-associated HC<sup>2,17,34</sup>.

As mentioned above, late-onset HC after SCT can also be caused by other viruses such as adenovirus, CMV, JC virus, and human herpes virus 6<sup>4,7,26,40</sup>. Therefore, blood PCR analyses, urinary PCR analyses, and urine cultures for other viruses should also be considered in SCT recipients with late-onset HC (Fig. 1).

## Treatment of HC

Many therapeutic modalities have been applied in HC; however, standard therapeutic guidelines have yet to be established<sup>22,35</sup>. In addition, evaluating the efficacy of these diverse modalities in clinical trials is complicated by their frequent concurrent administration<sup>35</sup>. Treatments can be selected based on the patient's general condition and HC grade, and most patients recover with conservative care<sup>11</sup>. Cases that do not respond to conservative care should receive intravesical therapy or systemic therapy (Table 2). Finally, surgical therapy can be considered if hemorrhage and urinary tract complications do not improve with medical therapy. A proposed diagnostic and therapeutic algorithm for SCT recipients with HC is shown in Fig. 1.



**Fig. 1.** Diagnostic and therapeutic algorithm for stem cell transplant recipients with hemorrhagic cystitis. SCT, stem cell transplantation; BKV, BK virus; JCV, JC virus; CMV, cytomegalovirus; PCR, polymerase chain reaction. \*See Table 1. †For BKV: urinary BKV DNA titer >10<sup>7</sup> copies/mL and serum BKV DNA titer >10<sup>4</sup> copies/mL.

### 1. Conservative care

It is necessary to reduce or stop immunosuppressive therapies in patients with BKV-associated HC<sup>35</sup>. However, this cannot be achieved in most patients due to the possible aggravation of GvHD. Therefore, analgesic therapy and intensive intensive intravenous hydration (3 L/m<sup>2</sup>/day) with forced diuretics are administered as an initial treatment<sup>11,22</sup>. In addition, a platelet count >50,000/μL and hematocrit >25% should be maintained via blood transfusion<sup>11,22,35</sup>. If HC symptoms do not respond to these therapies or blood clots form in the bladder, continuous bladder irrigation with normal saline through a three-way urethral catheter should be performed<sup>22</sup>.

### 2. Cystoscopy

If hemorrhage does not improve or a urinary tract obstruction develops after 3 to 4 days of conservative care, cystoscopy for the complete evacuation of blood clots should be performed<sup>22</sup>.

### 3. Intravesical therapy

If hemorrhage lasts for 7 to 10 days even after applying the aforementioned therapies, the intravesical instillation of topical

**Table 2.** Systemic therapies for BK virus-associated hemorrhagic cystitis in pediatric stem cell transplant recipients

Treatment	Comments	References
Intravenous cidofovir	Standard dose: 5 mg/kg weekly for two weeks, then biweekly with oral probenecid	26
	Low dose: 1 mg/kg 1–3 times weekly without oral probenecid	2, 50
Oral leflunomide	Loading dose: 100 mg/1.73 m <sup>2</sup> /day	54
	Maintenance dose: 10–20 mg/day according to body weight No reported studies in pediatric stem cell transplantations	
Oral/intravenous ciprofloxacin	500 mg twice a day (oral)	46
	200 mg twice a day (intravenous)	
	Contraindicated for children younger than 18 years of age	
Oral conjugated estrogen	Only case series	27
Hyperbaric oxygen	Requires special equipment	57

agents should be considered<sup>22</sup>. Formalin, alum, prostaglandins, fibrin glue, and hyaluronic acid have all been applied intravesically as topical agents for HC<sup>7-9,23,41,42</sup>, but their efficacies have yet to be investigated in controlled studies. The use of formalin in children should be restricted due to the potential for severe complications including suprapubic pain, bladder scarring, and subsequent fibrosis and contracture<sup>22,43</sup>. While alum does not cause these local complications, the systemic absorption of aluminum may cause encephalopathy, seizures, and acidosis<sup>22,44,45</sup>.

#### 4. Cidofovir

Cidofovir is a cytidine nucleoside analog and an effective antiviral agent. Cidofovir has been shown to inhibit intracellular BKV replication *in vitro*<sup>46,47</sup>. In addition, multiple studies have demonstrated the clinical and microbiological effects of intravenous cidofovir on BKV-associated HC<sup>2,26,38,48-50</sup>. In our hospital, all 11 pediatric SCT recipients who received intravenous cidofovir therapy showed a clinical response, and 10 of the recipients showed a microbiological response<sup>20</sup>. Importantly, no severe side effects of cidofovir were observed<sup>20</sup>. Nevertheless, the therapeutic efficacy of cidofovir has not been comprehensively confirmed through controlled studies, and the most appropriate dosing regimen (1 mg/kg vs. 5 mg/kg) is still unclear. In addition, the nephrotoxicity of cidofovir should be considered in SCT recipients who receive several nephrotoxic drugs concomitantly.

#### 5. Leflunomide

Leflunomide, which is used in the treatment of rheumatoid arthritis, suppresses immune responses by inducing cytostasis, particularly in activated lymphocytes<sup>51,52</sup>. Since BKV relies on host factors for its replication, leflunomide is generally assumed to inhibit BKV replication by inhibiting DNA replication in BKV-infected cells<sup>51</sup>. The clinical and microbiological effects of leflunomide on BKV-associated HC in adult SCT recipients have been reported<sup>53</sup>. However, reports of its efficacy in children have been limited to kidney transplantation recipients<sup>54</sup>.

#### 6. Ciprofloxacin

Although the quinolones are well-known as antibacterial drugs, they are also believed to inhibit intracellular BKV replication by inhibiting topoisomerase activity in BKV-infected mammalian cells<sup>55,56</sup>. The prophylactic and therapeutic effects of ciprofloxacin on BKV-associated HC in adult SCT recipients have been reported<sup>36,46</sup>. Quinolones are contraindicated in children younger than 18 years, and therefore, the effects of quinolones have not been studied in pediatric SCT recipients.

#### 7. Estrogen

Estrogen has shown therapeutic efficacy against HC in children;

it is believed that estrogen exerts these effects by stabilizing the microvasculature<sup>22,27</sup>. However, the evidence base consists of only a case report and a case series, neither of which was a controlled study. Moreover, other investigators have reported that estrogen is ineffective against HC<sup>7</sup>.

#### 8. Hyperbaric oxygen

High-pressure oxygen generates a high oxygen gradient between the damaged urothelium and the surrounding healthy tissues. This oxygen gradient promotes macrophage invasion into the damaged tissues and stimulates angiogenesis and tissue healing via the secretion of cytokines by macrophages<sup>57</sup>. Therapeutic effects have been reported in adults and children with HC after SCT<sup>8,38,57</sup>, but only in case series and case reports. Moreover, this treatment requires specialized equipment for supplying high-pressure oxygen.

#### 9. Surgical therapy

If HC is refractory to medical therapies, it may be treated with surgical interventions. Supravescical urinary diversion using a bilateral nephrostomy has shown efficacy in children with HC unresponsive to conservative care and intravesical therapy<sup>43</sup>. Supravescical urinary diversion prevents urokinase, which is secreted from renal cells, from reaching the bladder wall, thereby promoting bladder hemostasis<sup>43</sup>. Unfortunately, a life-threatening hemorrhage may require the selective embolization of vesical arteries or internal iliac arteries, and even cystectomies<sup>58,59</sup>. The proper indications and therapeutic efficacies of these surgical therapies have not yet been defined. Thus, future studies of surgical therapies for HC are required.

## Conclusions

Although pediatric SCTs have been performed for approximately 30 years, only a few studies of HC, an SCT-related complication, have been reported in Korea. It is possible to predict the development of BKV-associated HC after SCT using urinary and blood BKV DNA titers. However, no standard guidelines for prophylactic or preemptive therapies have been established. A standard treatment for BKV-associated HC has also not been established. Therefore, various therapies are administered to patients based on the attending physician's decision. More studies aimed at establishing appropriate diagnostic and therapeutic guidelines for BKV-associated HC are necessary. Such efforts should be helpful in reducing SCT-related complications and mortality in SCT recipients.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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