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Case report

# Successful treatment with intravesical cidofovir for virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation: A case report and a review of the literature

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ABSTRACT

Virus-associated hemorrhagic cystitis (VAHC) is a formidable complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The standard management of severe VAHC after allo-HSCT has not been established. Intravenous administration of cidofovir (CDV), an acyclic nucleoside analogue with broad-spectrum activity against DNA viruses, has been reported to be effective for VAHC, but it can cause severe renal toxicity. Here we report four cases who achieved clinical responses with intravesical instillation of CDV for severe VAHC after allo-HSCT. Median age was 57 years (40–63), and all were male. The underlying diseases were hematological malignancies. Three had received bone marrow transplantation, and one received cord blood transplantation twice. Conditioning regimen was myeloablative for one, and reduced-intensity for three. The viral types were BK virus and/or adenovirus. Two patients had received CDV intravenously prior to the intravesical therapy. A dose of intravesical CDV was 2–5 mg/kg. In all cases, symptoms of cystitis improved dramatically within a few days without showing any systemic adverse effects. The virological response was observed in two cases. This local therapy was effective even in the cases refractory to the intravenous CDV and a case with severe renal failure. Along with the review of literature, we propose that the intravesical instillation of CDV can be a therapeutic option for severe VAHC after allo-HSCT.



## 1. Introduction

Virus-associated hemorrhagic cystitis (VAHC) is a formidable and sometimes life threatening complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. Late-onset VAHC during the post-engraftment period is usually associated with BK virus (BKV) or adenovirus (ADV) infections with the incidence of 20–30% [1,2]. Busulfan dose, allogeneic bone marrow transplantation, and acute graft-versus-host disease (GVHD) grade $\geq$ II are reported risk factors for VAHC [3]. VAHC is clinically graded as follows: grade 1, microscopic hematuria; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with small blood clots; 4, massive macroscopic hematuria requiring instrumentation for clot evacuation and/or causing urinary obstruction [4]. In mild cases, VAHC is resolved spontaneously, through supportive measures (hyperhydration, forced diuresis, and bladder irrigation), or by reduction of the immunosuppressant. However, severe and refractory cases especially of greater than grade 2 require antiviral therapies. Several case reports and case series proved that intravenous administration of cidofovir (CDV), which is an acyclic nucleoside analogue with broad-spectrum activity against many DNA viruses [5], was effective for severe VAHC after allo-HSCT [6–9]. However, this treatment can cause considerable renal damage, which can be a serious concern for allo-HSCT patients who already have renal dysfunction caused by various drugs such as immunosuppressants and antibiotics and VAHC itself. In order to minimize its renal toxicity, intravesical instillation of CDV for VAHC was developed, and the first case was reported in 2005 [10]. However, its efficacy and safety have not been established yet. Here, we describe four cases of severe VAHC after allo-

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HSCT in our institute who underwent intravesical instillation of CDV. The treatment protocols were approved by the Ethics Committee of Kyoto University. Moreover, we review the literature on similar cases.

## 2. Case reports

### 2.1. Case 1

A 63-year-old man underwent bone marrow transplantation (BMT) from a recipient of matched unrelated donor (MUD) for acute myeloid leukemia during the second complete remission [Fig. 1a]. The conditioning regimen consisted of fludarabine (Flu; 25 mg/m$^2$, 5 days), intravenous busulfan (8.5 mg/kg, 2 days), and total body irradiation (TBI; 2 Gy). GVHD prophylaxis consisted of tacrolimus, methotrexate (MTX), and mycophenolate mofetil (MMF). On day 111, oral prednisolone (PSL; 15 mg/day) was initiated for chronic GVHD with liver dysfunction. On day 185, the patient developed pollakisuria and lower abdominal pain that worsened to severe VAHC with gross hematuria (grade 3). A polymerase chain reaction (PCR) assay detected ADV in his urine. The immunosuppressive therapy was reduced. From day 209, intravenous low-dose CDV (1 mg/kg) was initiated three times per week for a total of seven doses. However, the VAHC symptoms persisted. The bilateral hydronephrosis and the renal dysfunction developed, therefore, the intravenous CDV treatment was withdrawn. On days 265 and 283, intravesical CDV was performed. CDV (2 mg/kg) diluted in 100 mL normal saline was instilled into the bladder over 15 min via a urethral catheter that was subsequently clamped for 1 h. The gross hematuria and abdominal discomfort dramatically improved within a few days, the hydronephrosis resolved in one week and the microscopic hematuria disappeared in two weeks. The urinary frequency due to bladder irritation decreased from every 10 min to every 1 h. On day 292, ADV was undetectable in his urine.

### 2.2. Case 2

A 51-year-old man underwent BMT from MUD for acute lymphoblastic leukemia during the first complete remission [Fig. 1b]. The myeloablative conditioning consisted of cyclophosphamide (54 mg/kg, 2 days) and TBI (10 Gy). GVHD prophylaxis

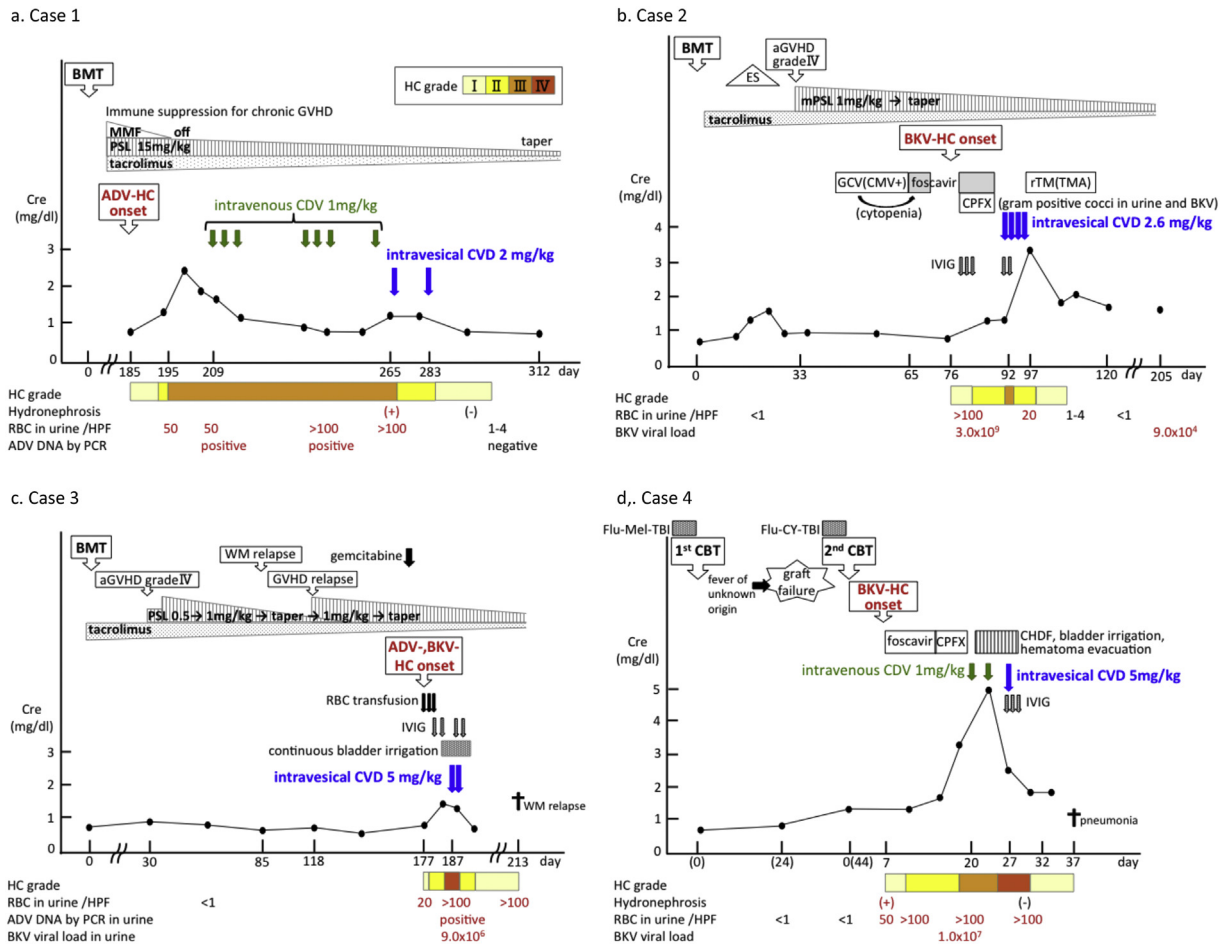


**Fig. 1.** Clinical courses. **a**. Case 1, a 63-year-old man with virus-associated hemorrhagic cystitis (HC) after allogeneic stem cell transplantation (allo-SCT) from an unrelated human leukocyte antigen (HLA)-identical donor for acute myeloid leukemia. **b**. Case 2, a 51-year-old man with virus-associated HC after allo-SCT from an unrelated HLA-identical donor for acute lymphoblastic leukemia. **c**. Case 3, a 63-year-old man with virus-associated HC after allo-SCT from an unrelated HLA allele-matched donor for Waldenström's macroglobulinemia (WM). **d**. Case 4, a 40-year-old man with virus-associated HC after a second cord blood transplantation from an HLA 4/6 allele-matched donor for non-Hodgkin lymphoma. **Abbreviations**: ADV-HC, adenoviral hemorrhagic cystitis; aGVHD, acute graft-versus-host disease; BKV-HC, BK virus hemorrhagic cystitis; BMT, bone marrow transplantation; CBT, cord blood transplantation; CDV, cidofovir; CHDF, continuous hemodiafiltration; CMV, cytomegalovirus; CPFX, ciprofloxacin; Cre, creatinine; CY, cyclophosphamide; DNA, deoxyribonucleic acid; ES, engraftment syndrome; Flu, fludarabine; GCV, ganciclovir; GVHD, graft-versus-host disease; HPF, high-power field; IVIG, intravenous immunoglobulin; Mel, melphalan; MMF, mycophenolate mofetil; mPSL, methylprednisolone; PCR, polymerase chain reaction; PSL, prednisolone; RBC, red blood cell; rTM, recombinant thrombomodulin; TBI, total body irradiation; TMA, thrombocytic microangiopathy.