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Case Report

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Rapid Virologic Response to Brincidofovir in Children with Disseminated Adenovirus Infection

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ABSTRACT

Disseminated adenovirus infections (d-ADV) after hematopoietic cell transplant (HCT) are often fatal with limited treatment options. Brincidofovir (BCV) a lipid ester of cidofovir is developed for this indication. We report four pediatric HCT recipients with d-ADV treated successfully with BCV.

Keywords: Brincidofovir; Antiviral treatment; Disseminated adenovirus; Hematopoietic cell transplant

INTRODUCTION

Adenovirus (ADV) infections may occur in up to 40% of pediatric HCT recipients [1]. T-cell depletion (TCD) (*ex vivo* CD34$^+$ or serotherapy with antithymocyte globulin or alemtuzumab), or severe graft-versus-host disease (GVHD) are associated with ADV infection post-HCT [2]. Recovery of ADV specific T-lymphocytes (ADV-CTLs) confers protection against ADV [3], whereas lymphopenia is a risk factor for disseminated ADV infection (d-ADV) [4]. *Ex vivo* by CD34$^+$ selection (Miltenyi Biotec, Gladbach, Germany) achieves a 5-log depletion of T-lymphocytes in the allograft [5]. D-ADV infections after TCD HCT are often fatal with mortality rates ranging from 50 - 100% [6-8].

There is currently no approved treatment for ADV. Intravenous cidofovir (CDV) is commonly used; however its utility is limited by associated nephrotoxicity [9]. Adoptive transfer of ADV-CTLs has shown efficacy in single center studies [2].

Brincidofovir (BCV) is a lipid-linked derivative of CDV with high potency against all clinically significant ADV subtypes and no evidence of renal or hematological toxicity to date [10, 11]. In lymphocyte-depleted pediatric HCT recipients with ADV infections, treatment with BCV resulted in faster and greater virologic responses to BCV compared with CDV [12]. BCV has been associated with gastrointestinal toxicity with typical onset after 4 - 6 doses of BCV [11]. Children may tolerate BCV better than adults possibly due to a more rapid turnover of gastrointestinal mucosa compared with adults [10].

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Conflict of Interest
GAP has been an investigator for Shire, Merck, Chimerix and Astellas and has received consulting fees from Shire, Merck, Chimerix and Astellas.

Author Contributions
Conceptualization: GAP, YJL. Data curation: SYC, SEP, FB, GAP, YJL, YJL. Writing - original draft: SEP, FB, GAP, YJL.

We describe 4 pediatric TCD HCT recipients with d-ADV infection treated successfully with oral BCV 2 mg/kg twice per week under Emergency Investigational New Drug from 9/2015 and 5/2016. The study was reviewed and approved by the Memorial Sloan Kettering Cancer Center Institutional Review and Privavy Board and granted a waiver of authorization (IRB #16-844). **Table 1** shows the clinical and virologic characteristics. Virologic responses to BCV are shown in **Figure 1A-1D**.

CASE REPORT

ADV PCR was performed by Viracor-Eurofins (Lee's Summit, MO, USA). The linear range of quantification of ADV PCR in the blood was $100 - 1 \times 10^{10}$ copies/mL. D-ADV was defined as previously defined [7].

1. Case A

A 19-month-old girl with severe combined immunodeficiency syndrome received a TCD HCT from a matched unrelated donor (MUD). Her post-transplcant course was complicated

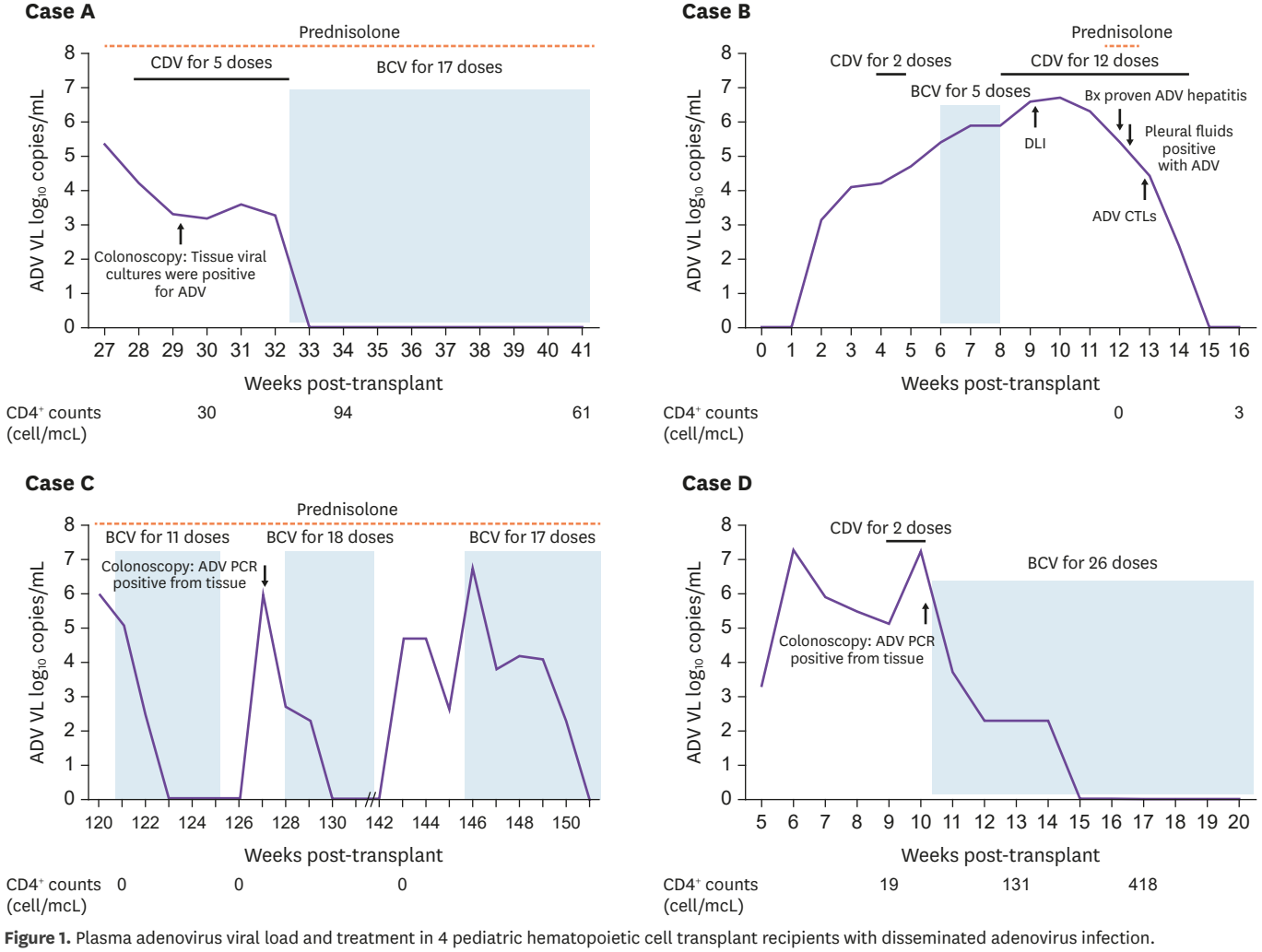

Figure 1. Plasma adenovirus viral load and treatment in 4 pediatric hematopoietic cell transplant recipients with disseminated adenovirus infection.
CD4+ count: cell/mcL.
CDV, cidofovir; BCV, brincidofovir; ADV, adenovirus; VL, viral load; DLI, donor lymphocyte infusion; CTL, cytotoxic T-lymphocyte; PCR, polymerase chain reaction.

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Table 1. Characteristics and outcome of disseminated adenovirus cases

Case	Age/ sex	Dx	Transplant type, donor	Post-transplant complications before onset of ADV viremia, immunosuppressant	First ADV viremia[a], days post-HCT (D)	Max ADV viremia, D	Sites of ADV	ADV disease, D	ADV viremia at first CDV Tx	ADV viremia at first BCV Tx	BCV initiation, D	Anti-viral Tx	Time to virologic clearance from BCV, days	ALC / CD4+ (cell/mcL) at BCV Tx	Outcome
A	19m/F	SCID	1st HCT: BMT, haplo mother (graft failure) 2nd HCT: $CD34^+$ TCD PBSCT, MUD	Autoimmune Hemolytic Anemia, Rituximab, Prednisolone	2.1×10^5, D+192	2.1×10^5, D+192	Blood, Stool, Urine	Probable Enterocolitis, D+207	4.3×10^4	<190	D+193	CDV IV 5 mg/kg × 5 doses BCV PO 2 mg/kg TIW × 17 doses	3	ALC 400 CD4+ 30	Alive
B	4y/M	ALL	$CD34^+$ TCD PBSCT, 9/10 MUD		469, D+10	4.7×10^6, D+69	Blood, Stool, Liver, RESP, Pleural Fluid	Definite Pneumonitis, D+84; Definite Hepatitis, D+88	5.8×10^4	3.3×10^5	D+25	CDV IV 5 mg/kg × 14 doses BCV PO 2 mg/kg TIW × 5 doses DLI, ADV CTLs	N/A	ALC 400 CD4+ 0	Alive
C	3y/M	Familial HLH	$CD34^+$ TCD PBSCT, Haplo mother	Skin Grade 3 GVHD and GI Grade 1 GVHD, Mesenchymal stem cell infusion, Alemtuzumab, CNI and Prednisolone	9.8×10^5, D+841	6.7×10^6, D+1026	Blood, Stool, RESP	Possible Enterocolitis, D+870	N/A	4.1×10^5	D+848	BCV PO 2 mg/kg TIW × 29 doses	1st course: 14 2nd course: 20	1st course: ALC 100 CD4+ 0 2nd course: ALC 100 CD4+ 0	Death, D+1088, MSOF
D	3y/F	ALL	1st HCT: $CD34^+$ TCD PBSCT, MUD 2nd HCT: $CD34^+$ TCD PBSCT, MUD	Acute Rejection of first allo-graft 2nd HCT: Alemtuzumab 1 mg/kg divided in 5 doses after 2nd HCT	2×10^3, D+38 (From 2nd HCT)	1.9×10^7, D+42 (From 2nd HCT)	Blood, Stool, Liver	Possible Enterocolitis, D+65 (From 2nd HCT)	2.8×10^5	1.6×10^7	D+57 (From 2nd HCT)	CDV IV 5 mg/kg × 2 doses BCV PO 2 mg/kg TIW × 26 doses	34	ALC 300 CD4+ 19	Death, D+539 (From 2nd HCT), relapse of primary disease

[a]ADV PCR in blood was performed by Viraco Eurofins (Lee's Summit, MO, USA). Values are copies/ml.

m, months-old; F, female; y, years-old; M, male; Dx, diagnosis; SCID, severe combined immune deficiency; ALL, acute lymphoblastic leukemia; HLH, hemophagocytic lymphohistiocytosis; HCT, hematopoietic cell transplant; BMT, bone marrow transplant; Haplo, Haploidentical; TCD, T Cell-depleted; PBSCT, peripheral blood stem cell transplant; MUD, matched unrelated donor; ADV, adenovirus; GVHD, graft-versus-host disease; GI, gastrointestinal; CNI, calcineurin inhibitors; D, day from transplant; max, maximum, RESP, respiratory specimens (bronchoalveolar lavage, nasopharyngeal swab); CDV, cidofovir; Tx, treatment; N/A, not applicable; BCV, brincidofovir; IV, intravenous; PO, orally; TIW, three times per week; DLI, donor lymphocyte infusion; CTLs, cytotoxic T lymphocytes, ALC, absolute lymphocyte counts; MSOF, multisystem organ failure.

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by autoimmune hemolytic anemia treated with prednisolone and 6 doses of rituximab. Six months post-transplant she presented for hypoactivity, irritability and watery diarrhea. On admission, stool ADV PCR was positive and ADV viremia was 2.1×10^5 copies/ml. She was treated with CDV and intravenous immunoglobulin. After 2 weeks of CDV, colonoscopy was performed. Pathology showed friable colonic mucosa. Viral culture from tissues was positive for ADV. Because of persistent diarrhea after 5 doses of CDV, BCV was started. ADV viremia became undetectable after 2 doses of BCV. BCV was stopped at 8 weeks after BCV initiation.

2. Case B

A 4-year-old boy with acute lymphoblastic leukemia (ALL) received a TCD HCT from a MUD. On Day 0, stool ADV PCR was positive and ADV viremia was negative. On Day +10, ADV viremia was 469 copies/ml and on Day +17 ADV viremia rose to 5.8×10^4 copies/ml. On Day +25, CDV was started due to persistent fever, diarrhea and rising ADV viremia. After 2 doses of CDV, CDV was switched to BCV due to increased ADV viremia (3.3×10^5 copies/ml). On Day +39, BCV was discontinued after 5 doses due to persistent diarrhea. CDV was resumed, however ADV viremia increased to 4.7×10^6 copies/ml on Day +69 and transaminitis was noted. Liver biopsy on Day +84 confirmed GVHD with ADV hepatitis (positive ADV stain). Concurrently, he developed respiratory distress and a nasopharyngeal swab was positive for ADV by PCR. On Day +88, thoracentesis was performed due to worsening pleural effusion. Pleural fluid was positive for ADV (1.8×10^5 copies/ml). He was treated with donor lymphocyte infusion (DLI) and subsequently with ADV-CTLs with virologic response.

3. Case C

A 3-year-old boy with familial hemophagocytic lymphohistiocytosis was admitted with fever, diarrhea and vomiting 2 years post-transplant. He received a TCD HCT from his haploidentical mother. His post-transplant course was complicated by poor graft function, refractory skin and gastrointestinal GVHD, human herpesvirus-6 viremia and chronic renal dysfunction. He received cyclosporine, tacrolimus, steroids and mesenchymal stem cells infusion for GVHD. On admission, cefepime and vancomycin were empirically started. Stool was negative for *Clostridioides difficile*. Symptoms persisted during admission. On hospital day 21, stool ADV PCR was positive and ADV viremia was 9.8×10^5 copies/ml. BCV was initiated. Viral clearance was achieved after 5 doses BCV and BCV was continued for 4 weeks. One week after BCV discontinuation, ADV viremia recrudesced to 1.0×10^7 copies/ml. BCV was reinitiated and continued for 10 weeks with good virologic control. Due to persistent diarrhea, colonoscopy was performed and pathology showed persistent gut GVHD. The tissue was positive for ADV by PCR. He received a stem cell boost 2 months after stopping BCV for poor graft function. He subsequently developed relapse of ADV viremia (6.7×10^6 copies/ml), thus BCV was resumed and ADV viremia became undectable after 7 doses of BCV. His hospital stay was further complicated by hospital-acquired pneumonia with respiratory failure. Despite resolving ADV viremia, he died due to multi-organ failure.

4. Case D

A 3-year-old girl with ALL received a TCD HCT from a MUD complicated by graft rejection and followed by a second TCD HCT from a different MUD one month after the first HCT. Her post-transplant course was complicated by Epstein-Barr virus (EBV) viremia treated with rituximab and cytomegalovirus viremia. On Day +38 post-transplant, she was found to have ADV viremia (2.0×10^3 copies/ml). On Day +42, ADV viremia increased to 1.9×10^7 copies/ml. On Day +53, she developed watery diarrhea and nausea. Stool ADV PCR was positive. On Day +56, colonoscopy was performed. The tissue was positive for ADV by PCR. On Day +56, ADV viremia was 2.8×10^5 copies/ml and CDV was started. After two doses of CDV, ADV viremia

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was 1.1 × 10^5 copies/ml. She developed worsening hepatic function. Computed tomography of the chest and abdomen on Day +65 showed a necrotic liver lesion and a necrotic lung mass. ADV viremia rose up to 2.3 × 10^7 copies/ml on Day +66 despite CDV. Lung and liver biopsies performed on Day +67 yielded *Legionella pneumophila* serotype 1 by culture and liver biopsy was positive for EBV and ADV by PCR. ADV viremia was 1.6 × 10^7 copies/mL on Day +69. On Day +71, levofloxacin was started for Legionella pneumonia and BCV for d-ADV infection. ADV viremia became undectable 34 days after initiation. She received BCV for 80 days as outpatient.

DISCUSSION

We report 4 pediatric TCD HCT recipients (overall 6 episodes of ADV viremia) with d-ADV treated with BCV. All patients were highly immunosuppressed, with profound lymphopenia and/or very low CD4 counts. Despite high ADV viremia (median 3.7 × 10^5 copies/mL) at BCV initiation, 3 of 4 patients cleared ADV viremia at a median of 14 days (range, 1 - 34) of BCV treatment. Two patients (cases A and C) were on high dose steroids. Two patients had received prior CDV treatment (case A and C) without response prior to BCV treatment. Three patients tolerated prolonged doses of BCV (range, 17 - 29 doses).

Case C had lymphopenia (100 cell/mm^3) and $CD4^+$ count was 0 cell/mm^3 during ADV infection. Despite a rapid virologic response to BCV, ADV recurred after discontinuation of BCV highlighting the importance of immune recovery for control of ADV infection. Importantly the patient responded rapidly after 2 short subsequent courses of BCV suggesting that repeated episodic treatment with BCV guided by ADV viral load (VL) remains effective even in the setting of persistent lymphopenia.

D-ADV infections are associated with substantial morbidity and mortality in HCT recipients [6-8]. Cases A, C and D with ADV colitis cleared ADV viremia with BCV. Case B did not tolerate BCV. BCV was discontinued after 5 doses concerning for gastrointestinal toxicity. Case B developed ADV hepatitis and ADV pneumonitis while on CDV. Case B responded to DLI and ADV-CTLs. While ADV-CTLs have shown safety and efficacy in small series (reviewed in reference 2), at present several hurdles preclude the broad applicability of this potentially effective therapy [2].

The virologic responses in our cases confirms the virologic activity of BCV even in lymphopenic patients and are in agreement with results of the recent BCV trial [11]. In that trial virologic responses were better, if BCV treatment was initiated at low VL and was associated with improved survival [11]. Our patients had high VL at BCV initiation despite which, 3 of 4 patients achieved virologic responses. One patient discontinued BCV due to gastrointestinal symptoms. Gastrointestinal toxicity is a known side effect of BCV [10]. Management of gastrointestinal toxicity due to BCV like case B is particularly challenging in patients with ADV in the gastrointestinal tract as symptoms may be related to ADV enteritis/colitis and/or BCV. Case B had diarrhea prior to BCV initiation and had persistent diarrhea while on BCV which led a clinician to stop BCV. An intravenous formulation of BCV is currently in development and may alleviate concerns for gastrointestinal toxicity.

In conclusion, our small case series show rapid virologic responses after short courses of oral BCV in 3 of 4 pediatric patients with d-ADV. Repeated short courses of BCV were effective in a patient with recurrent ADV viremia. Our data supports the study design of short-course oral BCV treatment in pediatric HCT recipients with ADV infection.

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