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Adenoviral Infections and a Prospective Trial of Cidofovir in Pediatric Hematopoietic Stem Cell Transplantation

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ABSTRACT

Adenoviral (ADV) infections are increasingly recognized as a cause of morbidity and mortality in pediatric hematopoietic stem cell transplantation (HSCT). We reviewed our experience with ADV infections in HSCT patients hospitalized for transplantation at Childrens Hospital Los Angeles January 1998 through December 1998. ADV was detected in 47% of patients, with recipients of HSCT from alternative donors (matched unrelated, unrelated cord, and mismatched related donors) being more frequently culture positive than recipients of HSCT from matched siblings (62% versus 27%, *P* = .04). Detection of ADV from 2 or more sites was associated with organ injury, eg, hemorrhagic cystitis, enteritis, and hepatitis. Because of the high incidence of ADV culture–positive patients and the lack of effective anti-ADV therapy, we initiated a prospective trial to evaluate cidofovir (CDV) in the treatment of ADV infections in HSCT recipients. Eight patients were enrolled on a dosage schedule of 1 mg/kg 3 times weekly. All of these patients eventually achieved long-term viral suppression and clinical improvement, although 6 patients needed prolonged CDV therapy for up to 8 months before CDV could be stopped without ADV recurrence. We did not observe dose-limiting nephrotoxicity, and the discontinuation of the drug was not required in any patients. Prospective controlled trials to further define the role of CDV in the treatment of ADV infections in HSCT patients are warranted.

KEY WORDS

Hematopoietic stem cell transplantation • Adenoviral infections • Cidofovir

INTRODUCTION

Adenoviral (ADV) infections have increasingly been recognized as a cause of morbidity and mortality in patients with immunologic deficiencies [1,2], especially following hematopoietic stem cell transplantation (HSCT) [3,4]. The incidence of cytomegalovirus (CMV) infection has diminished in HSCT recipients due to effective prophylactic antiviral therapies, and ADV infections have emerged as a major viral pathogen [2,4-6]. Epidemiologic studies have shown that pediatric patients who are recipients of matched unrelated donor HSCT or who have graft-versus-host disease (GVHD) are at increased risk of developing ADV infections [2,3,7-10]. It is uncertain at present whether ADV infections in HSCT recipients are due to reactivation of latent virus, donor derived acquisition, or horizontal transmission [11].

The clinical manifestations of ADV infections in HSCT recipients range from asymptomatic excretion to disseminated disease with multiorgan failure and death. Many infected recipients have clinical disease, including hemorrhagic cystitis, gastroenteritis, pneumonitis, hepatitis, and encephalitis [2,8,9]. Isolating virus from ≥2 sites has been found to correlate with invasive disease and an unfavorable clinical outcome [2,6]. Recent reports of mortality rates have ranged from 7.7% to 38% [4,7-9]. At present, no proven antiviral therapy is available for the treatment of ADV. However, ribavirin, ganciclovir, vidarabine, intravenous (IV) immunoglobulin, and adoptive immunotherapy/leukocyte transfusions have been administered empirically to ADV-infected immunocompromised patients, including HSCT recipients [9,11-21].

Cidofovir (CDV), a nucleoside and phosphonate analogue, is a broad-spectrum anti-DNA viral agent [22]. The active intracellular diphosphate form of the drug exerts its mechanism of action as both a competitive inhibitor and an alternative substrate for 2′-deoxycytidine 5′-triphosphate in the viral DNA polymerase reaction. CDV has been shown to

Table 1. *Underlying Diseases for Which Hematopoietic Stem Cell Transplantations Were Performed**

Underlying Diagnosis	No. of Patients
Acute lymphoblastic leukemia	12
Severe combined immunodeficiency	5
Acute nonlymphoblastic leukemia	4
Severe aplastic anemia	3
Wiskott-Aldrich syndrome	3
Non-Hodgkin's lymphoma	2
Chronic myelogenous leukemia	2
X-linked lymphoproliferative disorder	1
Chronic granulomatous disease	1
CD40 ligand deficiency	1
Fanconi's anemia	1
Juvenile chronic myelogenous leukemia	1
Total	36

*Retrospective review of adenoviral infections in hematopoietic stem cell transplant recipients from January 1998 to December 1998.

be curative in a preclinical model of ocular ADV in rabbits [23], and case reports have demonstrated some success in the treatment of disseminated ADV in immunocompromised patients (eg, HSCT recipients and acquired immune deficiency syndrome patients) [24,25] at the dosage of 5 mg/kg per week. The therapy had to be discontinued in 1 patient due to renal toxicity [24]. The dose-limiting toxicity of intravenous CDV, given at the recommended dosage of 5 mg/kg once a week, is nephrotoxicity, including an elevation in the serum creatinine levels and/or acute renal failure, proteinuria, and renal Fanconi syndrome with tubular acidosis. The concomitant use of IV hydration and probenecid can prevent or decrease the severity of adverse renal events. Probenecid decreases renal clearance of CDV by the active inhibition of renal tubule secretion. This action increases the serum levels of CDV and decreases its urinary concentration, thus improving its bioavailability and protecting the renal tubules [26]. Other side effects associated with the use of CDV include neutropenia and ocular toxicity (anterior uveitis, iritis, hypotony).

Pediatric patients with disseminated ADV infection treated with CDV at a dosage of 1 mg/kg 3 times a week became culture negative with the resolution of symptoms after 2 to 3 weeks of therapy (R. Whitley, oral communication, June 1999). This dosage was chosen in an attempt to reduce the renal toxicity associated with the previous dosing regimen (5 mg/kg once weekly) in a group of patients likely to have compromised renal function at the onset. We, therefore, initiated a prospective open-label trial evaluating the role of CDV at a dosage of 1 mg/kg 3 times a week for the treatment of ADV infections in HSCT recipients.

MATERIALS AND METHODS

Two studies are described in this article, a retrospective review of our experience with ADV in HSCT recipients (January 1998 through December 1998) followed by a prospective trial to evaluate CDV in the treatment of ADV infections in HSCT recipients (June 1999-December 2000). For both studies, organ injury and disease attributed to ADV was based on consistent clinical symptoms with positive cultures (pneumonitis, hemorrhagic cystitis, encephalitis), or, in the absence of positive cultures from the site of disease, multiple sites positive for ADV and the absence of another defined pathogen (enteritis, hepatitis, bone marrow suppression).

Review of ADV Infections in HSCT Recipients

A retrospective chart review of allogeneic HSCT recipients who were hospitalized from January through December 1998 was performed. The following data were collected: (1) demographic features (age at time of HSCT, sex), (2) underlying lymphohematologic disease, (3) type of HSCT: alternative donors (AD) (matched unrelated, unrelated cord, and mismatched related donors) or matched related donors (MRD), (4) sites of ADV culture positivity, (5) time to first positive ADV culture, (6) associated organ injury, and (7) clinical outcome (Tables 1-3).

CDV Treatment of ADV Infections

A prospective open study was performed to evaluate CDV administration in HSCT recipients with positive ADV cultures (June 1999-December 2000). The protocol was approved by the Committee for Clinical Investigations of the hospital Institutional Review Board. Written informed consent was obtained from the parent or legal guardian of each recipient before enrollment into the study. The inclusion criteria were (1) recipients of AD HSCT with positive ADV cultures from any site, (2) recipients of histocompatible HSCT with positive blood cultures or positive cultures from 2 or more sites, or (3) any HSCT recipient with positive cultures and clinical evidence of ADV infection, such as hemorrhagic cystitis, pneumonia, hepatitis, or enteritis. The exclusion criteria were (1) hypersensitivity to probenecid and/or cidofovir and (2) age younger than 3 months.

The treatment regimen consisted of CDV, 1 mg/kg per day 3 times a week for 9 doses. Probenecid, 1.25 g/m^2

Table 2. *Adenovirus Cultures in Hematopoietic Stem Cell Transplant Recipients**

No. of hematopoietic stem cell transplantations	36
No. of patients with positive adenoviral cultures (%)	17 (47)
Median day of first positive culture (range)	Day 35 (day –10 to day 257)
No. of positive cultures on admission (%)	3 (8)
Sites of positive cultures	
Urine	14
Blood	12
Respiratory	10
Cerebrospinal fluid	1
Stool/rectal	3
Type of hematopoietic stem cell transplantation with positive cultures	
AD (%)	13/21 (62)†
MRD (%)	4/15 (27)

*Retrospective review of adenoviral infections in hematopoietic stem cell transplant recipients. AD indicates alternative donor (matched unrelated, unrelated cord, or mismatched related); MRD, matched related donor.

†Corrected chi-square test, 4.24; $P = .04$.

Table 3. *Clinical Outcomes of Patients With Positive Adenovirus Cultures (N = 17)**

Outcome	No. of Patients (%)
Organ dysfunction	
1 positive site	0/7 (0)
≥2 positive sites	10/10† (100)
Bone marrow suppression‡	11 (65)
Graft-versus-host disease	5 (29)
Hemorrhagic cystitis	6 (35)
Enteritis	3 (18)
Hepatitis	2 (12)
Pneumonitis	2 (12)
Encephalitis	1 (6)
Deaths attributable to adenovirus infection	2/17 (12)
Encephalitis	1
Hemorrhagic cystitis/pneumonitis	1

*Retrospective review of adenoviral infections in hematopoietic stem cell transplant recipients.

†$P < .01$, Fisher exact test (2-tailed).

‡Not explained by other causes.

by mouth, was given 3 hours before and 1 and 8 hours after CDV administration. IV hydration at 3 times maintenance was initiated 1 hour before and continued until 1 hour after the completion of the CDV infusion, followed by hydration at 2 times maintenance for an additional 2 hours after CDV infusion. Recipients were initially treated with 9 doses. In patients whose cultures remained positive while on CDV or became positive after cessation of CDV therapy, CDV was instituted for an additional 9-dose course and then continued on varying schedules until ADV cultures became sterile (Tables 4 and 5).

Patients were cultured for ADV from nasopharyngeal wash and/or throat, urine, stool, and blood at the time of admission for transplantation or when clinically indicated, and weekly thereafter. Previously positive sites were cultured prior to subsequent doses of CDV. When clinically indicated, other sites (bronchoalveolar lavage and small-bowel and colon endoscopy biopsies) were cultured. Creatinine clearance and glomerular filtration rate were obtained prior to initiation of CDV and at the completion of therapy. Drug toxicity was monitored with serum creatinine, urine protein, complete blood count with differential, and a chemistry panel.

Detection of Adenovirus

Adenovirus was detected using a shell-vial culture method [27]. Blood was collected in heparin or EDTA tubes, and a buffy coat was prepared and washed with sterile phosphate-buffered saline. Respiratory tract specimens were mixed with Hanks' balanced salt solution, vortexed, and, if necessary, centrifuged to remove particulate material. Urine specimens were inoculated directly or briefly centrifuged if turbid. Stool or rectal swabs were placed in viral transport medium and centrifuged in the case of the former or vortexed for the later. The viral transport media were then used for inoculation. Two shell vials with a monolayer of A549 cells were inoculated with 0.2 to 0.3 mL each of processed specimen. The vials were incubated for 16 to 24 hours and checked for toxicity. Incubation was continued for 40 to 48 hours, and the first vial was stained using an indirect immunofluoresence antibody assay with mouse anti-adenovirus monoclonal antibodies (ViroMed, Minneapolis, MN). The second shell vial was stained after 5 days of incubation if the first vial was negative. The stained cells were examined by fluorescence microscopy for cells with nuclei or nuclear-cytoplasmic staining.

Statistical Analyses

Differences between groups were assessed by chi-square or Student *t* test, with *P* values of <.05 considered significant,

Table 4. *Characteristics of Hematopoietic Stem Cell Transplant Recipients Treated With Cidofovir**

Patient No.	Diagnosis	Age at HSCT	Type of HSCT	HSCT Conditioning	GVHD Prophylaxis	GVHD Status at Time of Initial Positive ADV culture	Day of Initial Culture	Sites of Initial Positive ADV Culture
544	Aplastic anemia	8 y 1 mo	AD	CTX, ATG, TLI	CSA, MTX, ATG	Chronic skin and GI	540	U, TH
583	Hereditary lympho-histiocytosis	10 mo	AD	CTX, BU, VP16	CSA, MTX, ATG		–11	U, TH, N, S, BAL
597	Acute lymphoblastic leukemia	6 y 11 mo	MRD	TBI, ATG, VP16	MTX		–20	B
610	Acute lymphoblastic leukemia	7 y 7 mo	AD (cord)	CTX, ATG, TBI	CSA, MPS	Chronic skin and GI	44	U
616	Aplastic anemia	14 y 8 mo	AD	CTX, ATG, TLI	CSA, MTX, ATG	Acute and chronic	21	B
622	Myelodysplastic syndrome	3 y 1 mo	AD	CTX, ATG, BU	CSA, MTX, ATG		–5	U, NP
637	Chronic myelogenous leukemia	6 y 9 mo	AD	CTX, ATG, BU	CSA, MTX, ATG	Chronic skin and GI	52	U, TH
651	Chronic myelogenous leukemia	10 y 8 mo	MRD	CTX, BU	CSA, MTX		53	U, B

*HSCT indicates hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; ADV, adenovirus; AD, alternative donor; CTX, cytoxan; ATG, antithymocyte globulin; TLI, total lymphocyte irradiation; CSA, cyclosporine A; MTX, methotrexate; GI, gastrointestinal; U, urine; TH, throat; BU, busulfan; VP16, etoposide; N, nasopharyngeal; S, stool; BAL, bronchoalveolar lavage; MRD, matched related donor; TBI, total body irradiation; B, blood; MPS, methylprednisolone.

Table 5. *Clinical and Virologic Outcomes of Patients Receiving Cidofovir**

Patient No.	Clinical Disease Attributable to ADV	Culture Status After Initial 9 doses of CDV	New Sites Cx Positive (on CDV)	Recurrence (off CDV)†	Duration of Therapy	Pre-CDV BUN/CR (mg/dL)	Post-CDV BUN/CR (mg/dL)	Current Status
544	Febrile illness, enteritis, GVHD exacerbation	Negative		Yes	3 mo‡	23/0.6	26/0.7	Alive, Cx negative
583	Pneumonia	Negative		No	3 wk	22/0.2	14/0.2	Deceased 8 mo post-HSCT§
597	Asymptomatic	Positive		No	6 wk	14/0.4	26/0.6	Deceased 5 mo post-HSCT§
610	Enteritis, febrile illness, conjunctivitis, GVHD exacerbation	Negative	Blood, gastrointestinal (colon), nasopharyngeal	Yes	8 mo‡	18/0.6	8/1.1	Alive, Cx negative
616	Febrile illness, hemorrhagic cystitis, GVHD exacerbation	Negative	Blood	Yes	5 mo‡	58/1.2	15/1.1	Alive, Cx negative
622	Pneumonia, ARDS	Positive	Blood	No	2.5 mo	21/0.4	6/0.4	Alive, Cx negative
637	Febrile illness, enteritis, GVHD exacerbation	Negative		No	3 wk	9/0.4	15/0.3	Alive, Cx negative
651	Hemorrhagic cystitis	Positive		No	2 mo‡	11/0.6	8/0.5	Alive, Cx negative

*ADV indicates adenovirus; CDV, cidofovir; Cx, adenoviral culture; BUN, blood urea nitrogen; CR, creatinine; GVHD, graft-versus-host disease; ARDS, acute respiratory distress syndrome.

†Virologic and/or clinical recurrence after stopping CDV.

‡Patient required CDV 1 to 2 times per week for up to 3 months for suppression of disease and/or positive cultures.

§Death unrelated to ADV infection.

using EpiInfo version 6 (Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Incidence of ADV in HSCT Recipients

During the period from January through December 1998, 36 patients who received HSCT for lymphohematologic disease were hospitalized. Table 1 details the underlying diseases for which HSCT were performed. Twenty-one patients received HSCT from AD and 15 from MRD. The median patient age was 5.5 years (range, 3 months-19 years) with a male:female ratio of 21:15. Table 2 describes the ADV isolations. In 1998, 17 (47%) of 36 HSCT recipients developed positive ADV cultures from time of admission for transplantation through hospital discharge. Three of 17 patients had positive cultures at the time of admission and were clinically asymptomatic. When patients receiving AD HSCT were compared with patients receiving MRD HSCT, 62% of AD HSCT recipients had positive ADV cultures, whereas only 27% of MRD HSCT recipients had positive ADV cultures ($P = .04$; corrected chi-square, 4.24). Table 3 details the patients' outcomes in terms of morbidity and mortality. All 10 patients with ≥2 positive culture sites for ADV developed organ dysfunction, whereas none (0/7) of the patients with only 1 positive site developed organ dysfunction ($P < .01$). Concomitant bone marrow suppression (11 patients) unexplained by other causes (ganciclovir administration or other infections) and GVHD (5 patients) were associated with the development of ADV infection. There were 4 deaths in these patients, 2 of which were directly attributable to ADV infection: 1 from encephalitis and 1 from hemorrhagic cystitis/pneumonitis.

The Use of CDV in the Treatment of ADV

Eight recipients undergoing HSCT, 6 AD and 2 MRD, with positive ADV cultures were enrolled in a phase II trial of CDV. Table 4 describes the patient characteristics; 3 of 8 patients were ADV culture positive at the time of admission for transplantation. Two of the 3 pre-HSCT patients were symptomatic (pneumonia) and had multiple sites of ADV positivity. The third patient was asymptomatic, but had a positive blood culture. Additionally, 2 of 3 were to receive unrelated donor HSCT. All 3 patients were treated when culture results became available because, according to our experience from the previous year, the risk of disseminated disease due to ADV was very high, especially in the setting of an unrelated donor HSCT. The remaining 5 patients developed positive ADV cultures after HSCT (range, day 21-540). Positive ADV cultures were initially detected in urine (1), blood (2), nasopharyngeal wash/urine (1), throat/urine (2), urine/blood (1) and stool/bronchoalveolar lavage/urine/throat (1).

The clinical and virologic outcomes of patients receiving CDV are detailed in Table 5. Five of 8 recipients were ADV culture negative at the end of the initial 9 doses of CDV. The remaining 3 recipients remained ADV culture positive and continued to receive CDV therapy for an additional 9 doses. Three of the 5 patients, who had initially become culture negative, developed positive ADV cultures after the discontinuation of CDV, and CDV therapy was reinstituted; 2 of these patients received 2 additional courses (9 doses per course), and 1 received 1 additional course. All 3 patients who had ADV recurrences were receiving therapy for established GVHD. Overall, 6 of 8 patients had persistent positive ADV cultures or recurrence and required further CDV after completion of the initial course of CDV

therapy. Three of 8 patients had new sites of ADV culture positivity while receiving CDV therapy. After the completion of multiple (2-3) courses of CDV, 4 of 8 recipients required ongoing CDV therapy, administered 1 to 2 times weekly for up to an additional 3 months, to suppress viral production until immunologic recovery occurred.

All 8 patients in this study eventually became culture negative with cessation of ADV-related disease and without evidence of permanent ADV-related organ dysfunction. Two patients treated with CDV died of causes unrelated to ADV disease: 1 from sepsis/multiorgan failure and 1 from the relapse of acute lymphoblastic leukemia.

None of the patients required the discontinuation of CDV therapy for renal or other toxicities. Because of the complex nature of these patients and administration of other potentially nephrotoxic agents (eg, cyclosporin A, aminoglycosides), some patients did experience renal dysfunction (eg, patient number 610, Tables 4 and 5), but it could not be determined whether the dysfunction was directly attributable to CDV alone. Many patients experienced gastrointestinal symptoms, particularly nausea, associated with probenecid administration.

As previously reported, in addition to organ involvement, eg, pneumonitis, hemorrhagic cystitis, caused by ADV infection, the onset or exacerbation of acute and chronic GVHD was associated with the onset of positive ADV cultures. Three of the 4 patients who required long-term CDV therapy to maintain an ADV culture–negative status also required additional therapy to treat exacerbations of GVHD (declizumab [Zenapax], mycophenolate mofetil [Cellcept], and/or ATG [Atgam]).

DISCUSSION

In this retrospective study of pediatric patients hospitalized for HSCT for lymphohematologic diseases, positive ADV cultures were detected in 47% of recipients. Patients receiving HSCT from AD were more frequently ADV-culture positive than recipients of histocompatible transplants (62% versus 27%). Detection of ADV from 2 or more sites was associated with invasive disease. Of the 4 deaths that occurred among study patients, 2 were directly attributable to ADV disease. The detection of ADV in patients before or shortly after they undergo HSCT suggests that reactivation of latent virus may be the source of replicating ADV in some patients [28,29].

At present there is no established therapy for ADV infections. Indeed, 2 recent retrospective reviews of the use of intravenous ribavirin in adult HSCT recipients with invasive ADV infection did not show appreciable benefit [30,31]. In a recent study using CDV at the standard recommended dosage (5 mg/kg once a week), 3 of 7 pediatric patients experienced nephrotoxicity after the second dose of CDV, and therapy was interrupted [32]. Two patients tolerated reintroduction of therapy, but 1 patient died of invasive ADV after therapy was discontinued.

In our study, all 8 patients treated with CDV eventually became culture negative after 3 weeks to 8 months of CDV therapy. Since discontinuing therapy, all patients have remained culture negative (2-10 months). The small number of patients treated and the absence of a control group make the determination of the significance of these findings difficult. No deaths were attributable to ADV in patients receiving CDV, and sustained toxicity related to the use of CDV was not documented. The initial response to CDV did not predict the long-term response to therapy. Five of 8 patients had an initial rapid response to CDV, becoming culture negative; only 1 of these patients had a durable response to CDV therapy and required only 1 course of CDV. These results suggest that, as in the case of herpes infections in HSCT recipients, the long-term administration of antiviral therapy will be required, presumably until the HSCT recipient develops anti-ADV cellular immunity adequate to permit the successful cessation of CDV therapy.

Three patients, each of whom had coexisting GVHD, were treated with prolonged CDV therapy (range, 3-8 months) to suppress viral excretion. The presence of viral infection, most notably CMV, has long been recognized as a risk factor for the development of GVHD in HSCT recipients [33-41]. Our data, and that of others, suggest that a similar relationship may exist between ADV and GVHD [1,2,7,10]. It has been postulated that acute GVHD in the context of viral infections, such as those of the herpes group and others, is initiated by donor-derived T lymphocytes with reactivity to viral antigens expressed on host cells [42]. In chronic GVHD, which is associated with CMV infections, the development of autoantibodies to CD13, expressed on keratinocytes, fibroblasts, endothelial cells, and macrophage/monocytes, appears to be associated with the development of clinical disease [43]. Both acute and chronic GVHD may involve local donor- and recipient-derived cytokines (tumor necrosis factor α, interferon γ, interleukin [IL]-1α, IL-6), leading to the pathologic changes in the skin and gastrointestinal system [42,43]. In addition, the presence of viral infections may further suppress the immunocompetence of the developing donor-derived immune system [41].

During 1998, patients who underwent HSCT at Childrens Hospital Los Angeles (CHLA) experienced a high incidence of ADV culture positivity, which was associated with morbidity and mortality. The rate of ADV culture positivity at CHLA was higher than that published in other pediatric reports [7,8,10]. Ongoing studies are needed to define the epidemiology of ADV infections in pediatric HSCT recipients. Major limitations in the present study include the absence of a prospective control group and the inability to determine the serotypes, which would be helpful in the characterization of the epidemiology of ADV infections. In addition, the absence of histopathologic support for some clinical definitions of illness attributed to ADV, specifically enteritis and hepatitis, may have led to an overestimation of ADV disease. In this study, shell-vial assay was used for detection of ADV; other diagnostic tools (ie, quantitative nucleic acid amplification techniques) [44,45] should be investigated to determine their role in the diagnosis of ADV disease. Earlier and quantitative ADV detection may aid in the investigation of the response to new prophylactic and therapeutic interventions, as has been the case for CMV infection [46-50].

In the present study, CDV on the dosage schedule of 1 mg/kg per day administered 3 times weekly appeared to be well tolerated. In view of the pathogenic potential of ADV in HSCT recipients, prospective controlled trials to define further the role of CDV in the treatment of ADV infections in HSCT recipients should be considered.

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