MAJOR ARTICLE

Treatment of Adenovirus Infections in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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Retrospective analysis of 303 patients who underwent allogeneic hematopoietic stem cell transplantation identified 35 (11.5%) with adenovirus infection. Among them, 22 received specific therapy. As first-line therapy, 18 were treated with intravenous ribavirin, 3 with cidofovir, and 1 with vidarabine. Moreover, 2 received donor leukocyte infusion in combination with ribavirin, and 1 received it after failing to respond to other therapies. Seven survived (31.8%; 3 of 13 who received ribavirin alone and 2 of 3 who received cidofovir). Among the 5 patients treated with combined strategies, 2 who received donor leukocyte infusions showed clearance of all symptoms. Acute graft-versus-host disease grade $\geqslant 3$ ($P = .01$) and a long delay between infection and treatment ($P = .05$) correlated with a greater risk of treatment failure. In conclusion, ribavirin and vidarabine are ineffective options, particularly for patients at who are high risk of acquiring disseminated adenovirus disease. Conversely, cidofovir or donor leukocyte infusions seem to be encouraging approaches if initiated early.

The incidence of invasive adenovirus infections has been reported in as many as one-fifth of hematopoietic stem cell transplantation (HSCT) recipients over the past few years [1–7]. This probably is attributable to the increasing number of patients, particularly children, receiving unrelated or related HLA-mismatched T cell–depleted grafts [1, 4, 7].

No specific antiviral therapy of proven value currently exists for severe adenovirus infection in immunocompromised hosts, particularly in patients undergoing HSCT. Different antiviral regimens are used when adenovirus infection is suspected or diagnosed. They include intravenous immunoglobulins (IVIGs) alone [4] or in combination with ribavirin [1, 8, 9], ganciclovir, or vidarabine [10, 11], with anecdotal case reports of resolution of localized adenovirus disease in uncontrolled studies [12]. The outcome remains poor for patients with disseminated or invasive disease [1]. The recently reported successful treatment of adenovirus disease with cidofovir [13] or with donor leukocyte infusion (DLI) [14] is worth further consideration.

Here, we retrospectively describe our experience of treatment of adenovirus infection among 22 consecutive recipients (pediatric and adult patients) of allogeneic HSCT in our unit from May 1985 through November 1999.

PATIENTS AND METHODS

Patient characteristics. Adenovirus was isolated from 35 of 303 consecutive allogeneic HSCT recipients, with an overall incidence rate of 11.5% (table 1). Among those patients who developed adenovirus infection, 22 received specific therapy and 13 did not. As shown in table 2, most patients who were treated were

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Table 1. Incidence of adenovirus infection and disease (probable and definite), according to source of hematopoietic stem cell transplant (HSCT).

Type of HSCT	*n*	Infection	Disease	Mortality	Overall mortality
Matched sibling	222	5.4	1.8	0.9	16.6
MUD[a]	81	28	20.7	14.6	52
Total	303	11.5	6.8	4.6	41

NOTE. Data are percentage of patients, unless otherwise indicated. Disease, probable or definite disease; infection, asymptomatic infection; mortality, adenovirus-related mortality; overall mortality, mortality among patients with adenovirus infection; MUD, matched unrelated donor.

[a] Or mismatched family member.

children with hematologic malignancies. Most received unrelated ($n = 16$) or related partially HLA–matched grafts ($n = 3$). Eleven of these 22 patients underwent T cell–depleted bone marrow transplantation (BMT), and 86% received antithymocyte globulins either before the graft as prophylaxis for graft-versus-host disease (GVHD) and/or after the graft as GVHD treatment. Finally, 13 (59%) patients developed acute grade 2–4 GVHD.

The characteristics of the 13 untreated patients are summarized in table 2. Notably, in this group, more patients received matched sibling bone marrow ($n = 9$) and methotrexate combined with cyclosporin as GVHD prophylaxis. Moreover, fewer patients received antithymocyte globulins and none developed acute grade 3–4 GVHD.

Adenovirus detection and serotyping. Surveillance with use of the IDEIA test (Dako) and cultures of throat, nasopharynx, urine, stool, and conjunctiva were done twice weekly for most inpatients and weekly or every 2 weeks for most outpatients throughout the first 100 days after HSCT. Other samples (bronchoalveolar lavage fluid, blood, and CSF) were cultured as clinically indicated. Biopsy specimens were processed for routine histological studies; adenovirus was identified by characteristic histological changes and immunohistologically with fluorescent antibody staining. Moreover, adenovirus was sought in biopsy specimens by means of conventional culture on human diploid fibroblast cells and PCR assay. Adenovirus serotyping was done for 21 patients [15]. Serotypes 1 ($n = 6$), 2 ($n = 7$), and A31 ($n = 4$) were most commonly identified. Other serotypes detected were serotype 8 ($n = 1$), serotype 5 ($n = 1$), and serotype 3 ($n = 2$). Antibody activity of patients' and donors' serum against adenovirus antigens was not measured before transplantation.

Definition of adenovirus infection. Adenovirus infection was defined according to the adapted Wisconsin criterita [4]. Definite disease was defined by either the presence of adenovirus nuclear inclusions, by a positive result of tissue culture or PCR assay from a sterile site (excluding the gastrointestinal tract), or by a positive immunohistological study with compatible symptoms without other identifiable cause. Probable disease was defined as the presence of $\geqslant 2$ positive results of tissue culture or PCR assay from other body sites with compatible symptoms without other identifiable cause. Asymptomatic infection was defined as the presence of $\geqslant 1$ positive result of tissue culture or PCR assay from other body sites without compatible clinical symptoms.

Characteristics of adenovirus infections. Among the treated group ($n = 22$), 3 patients had definite and 12 had probable disseminated adenovirus disease. The clinical spectrum included enteritis ($n = 14$), hemorrhagic cystitis ($n = 5$), encephalitis ($n = 2$), hepatitis ($n = 2$), and pneumonia ($n = 2$; table 3).

The remaining 7 patients had adenovirus isolated at a single site (stool, 6; urine, 1) without compatible clinical symptoms. Adenovirus first was identified at a median of 44 days after HSCT (range, 5 days before to 184 days after). The median duration of positive culture results before treatment was 21 days (range, 11–40 days). Adenovirus was isolated at diagnosis of infection from a mean of 1.6 sites (range, 1–3 sites).

Among the untreated group ($n = 13$), the time between HSCT and the first isolation of adenovirus was 13–120 days after transplantation (median, 46 days). Overall, it was most commonly isolated from 1 site per patient. The median duration of positive culture results for the 11 patients whose adenovirus cleared spontaneously was 25 days (range, 10–60 days). Two patients had probable disease (colitis, 1; hemorrhagic cystitis, 1). The 11 other patients had adenovirus isolated from stool and were asymptomatic.

Treatment of adenovirus infections. Table 4 shows treatments that patients received for adenovirus infections. Eighteen patients (patients 1–18) received ribavirin as part of first-line therapy, 13 alone and 5 in association with other treatments (cidofovir, 1; vidarabine, 2; and DLI, 2). Among these patients, 2 (patients 8 and 12) were given 2 successive courses of ribavirin. Seven patients (patients 6, 7, 9, 12, 14, 16, and 18) received a second-line treatment after failure of this first-line therapy (vidarabine, 2; vidarabine plus cidofovir, 1; cidofovir, 2; vidarabine plus second course of ribavirin, 1; and DLI plus second course of ribavirin, 1). Finally, 1 patient (patient 9) received a third-line treatment (DLI) after failure of treatment with ribavirin, vidarabine, and cidofovir. Three of these 18 patients treated with ribavirin were treated for definite disease, 10 for probable disease, and 5 for asymptomatic adenovirus infection.

Three patients received cidofovir only as part of first-line therapy (patients 21–23). Two had asymptomatic infection, and 1 received prophylactic cidofovir (patient 22). This latter patient underwent a familial haplo-identical HSCT for hemophagocytic

Table 2. Characteristics of patients in study of adenovirus infection among hematopoietic stem cell transplant (HSCT) recipients.

Characteristic	Patients	
	Treated (n = 22)	Untreated (n = 13)
Median (range) age, y	9.5 (1–19)	12.5 (3–51)
Age >18 y	20	5
Sex		
Male	11	10
Female	11	3
Type of disease		
Malignant	22	12
Nonmalignant	0	1
HSCT type		
Matched sibling	3	9
2d HSCT	2	1
Matched unrelated donor	16	3
2d HSCT	1	1
Mismatched family member	3	1
GVHD prophylaxis		
T cell depletion	11	2
Other[a]	11	11
Antithymocyte globulins		
Prophylactic	13	2
GVHD therapy	10	0
Acute GVHD		
⩾2	13	8
3–4	7	0
Chronic GVHD[b]	9/17	6/13
Type of adenovirus infection		
Definite disease	3	0
Probable disease	12	2
Asymptomatic infection	7	11

NOTE. Data are no. of patients, unless otherwise indicated. GVHD, graft-versus-host disease.

[a] Methotrexate and cyclosporine.

[b] For patients who survived >100 days.

lymphohistiocytosis in third complete remission after 2 unsuccessful unrelated transplantations. One patient (patient 19) received vidarabine alone as part of first-line therapy for probable disease.

Finally, 3 patients (patients 6, 9, and 18) received DLI ($1–5 \times 10^5$ $CD3^+$ cells/kg body weight) for life-threatening adenovirus disease either as first-line therapy (patients 6 and 18) associated with ribavirin or after unsuccessful therapy with ribavirin combined with vidarabine and cidofovir (patient 9). Patient 18 received 2 infusions (5×10^5 $CD3^+$ cells/kg each) on days 41 and 55 after HSCT.

Ribavirin was given iv at a loading dosage of 35 mg/kg followed by 25 mg/kg every 8 h for a total of 10 days. Cidofovir with concomitant probenecid was given iv at a dosage of 5 mg/kg each week for 2 weeks and then every 2 weeks for a total of 4 doses. Patient 22 received prophylactic cidofovir (5 mg/kg every 2 weeks) for 10 weeks (between day 60 and day 240 after HSCT). Vidarabine was given iv at a dosage of 10 mg/kg per day for 5 days in a 2–3-h infusion as 1 course.

Statistical analysis. Means were compared by the Student's t test or by the Mann-Whitney U test. Univariate analysis of risk factors associated with failure of antiviral therapy was done by use of the χ^2 and Fisher's exact tests. Factors reviewed included age of the patient, time between adenovirus infection and treatment, time of first positive culture result, staging of adenovirus infection, number of sites of infection, presence of acute GVHD, stem cell donor source, T lymphocyte depletion of the bone marrow, and administration of antithymocyte globulins.

RESULTS

Treated group. Thirteen patients received iv ribavirin as the only first-line treatment. All completed the full 10 days (table 4). Among them, 5 had asymptomatic adenovirus infection, 5 had probable disease, and 3 had definite disease. Two of the 5 with asymptomatic adenovirus infection (patients 1 and 4) recovered, and 3 (patients 5, 12, and 16) died, despite 2 receiving second-line therapy (1 each cidofovir and vidarabine). The treatment was successful initially for patient 16, but the infection eventually relapsed, and he died from adenovirus disease and acute GVHD. Two of the 5 patients with probable disease (patients 10 and 14) recovered, but patient 14 relapsed with adenovirus disease 167 days later. Ribavirin combined with vidarabine was readministered unsuccessfully. The other 3 patients with probable disease died, 2 from adenovirus disease (patients 9 [despite successive treatments including vidarabine, cidofovir, and DLI] and 13), and 1 (patient 11) from cytomegalovirus (CMV)-associated pneumonitis. All 3 patients with definite disease (patients 2, 3, and 7) died from adenovirus infection. In conclusion, only 3 of 13 patients who received ribavirin as the only first-line therapy survived, and 10 died from disseminated adenovirus disease, associated with acute GVHD (in 6 patients), graft failure (in 1 patient), or CMV-associated pneumonitis (1 patient).

Five patients, all with probable disease, received ribavirin in association with other treatments (patients 6, 8, 15, 17, and 18). Two survived, 1 of them (patient 6) was treated with ribavirin, DLI, and cidofovir, and the other (patient 8) was treated with the combination of ribavirin and cidofovir.

Of 3 patients given cidofovir as first-line therapy, 2 survived (patients 21 and 23). Both had asymptomatic adenovirus infection. One died (patient 22) from adenovirus disease, despite

prophylactic cidofovir administration. One patient (patient 19) unsuccessfully received vidarabine as the only first-line therapy for a probable adenovirus infection.

Clearance of virus excretion correlated with survival; indeed, 10 of 21 evaluable patients became culture-negative for adenovirus (median, 11 days; range, 7–35 days), and 7 survived. Conversely, none of the 11 patients who did not have clearance of adenovirus is still alive.

No serious adverse events were noticed during or after treatment with ribavirin. Only 1 of the 18 patients who received this treatment required more RBC transfusions than expected. Adverse effects of vidarabine, including myelosuppression, did not occur. However, in 1 patient (patient 22), cidofovir probably induced end-stage renal failure. At the onset of treatment, the recipient had proteinuria (protein level in urine $\leq$1.2 g/day) and decreased creatinine clearance (60 mL/min/1.73 m^2). Transient but progressive deterioration in renal function was observed after each cycle (6 doses during a period of 42 days). When cidofovir was started, he received concomitant nephrotoxic drugs (cyclosporine and amphotericin B). However, none of the 6 other patients treated with cidofovir experienced such renal failure, despite similar associated nephrotoxic drugs (cyclosporine, 3; foscarnet, 2; and lipid-associated amphotericin B [1–3 mg/kg/day], 6).

Finally, 3 patients received adoptive immunotherapy (DLI); 2 survived after treatment with DLI plus cidofovir (patient 6) or after 2 courses of DLI and ribavirin (patient 18). Clearance of virus excretion occurred 25 days after immunotherapy. One patient died (patient 9), despite 3 consecutive antiviral treatments (ribavirin, vidarabine plus cidofovir, and DLI). None of them showed evidence of GVHD or aplasia; nevertheless, 1 (patient 18) experienced fatal interstitial pneumonitis associated with thrombotic microangiopathy 70 days after the second course of DLI (total dose of $CD3^+$ cells, 1×10^6/kg body weight). At autopsy, neither infectious nor malignant causes could be demonstrated.

Untreated group. Thirteen patients did not receive specific treatment for asymptomatic adenovirus infection ($n = 11$) or probable disease ($n = 2$). Two of them died from disseminated adenovirus infection (1 each asymptomatic and probable disease), and 11 recovered with a median spontaneous clearance of virus excretion of 25 days (range, 10–60 days). Four other patients died from causes unrelated to adenovirus infection.

The 2 patient groups (treated or untreated) were not comparable. Indeed, the former included more patients with high-risk factors. There was a substantially higher proportion of children with high-grade adenovirus disease, recipients of unrelated or HLA-mismatched grafts, and patients receiving T cell–depleted bone marrow in combination with antithymocyte globulins.

Risk factors for treatment failure. There were significant

Table 3. Characteristics of adenovirus infection among patients undergoing hematopoietic stem cell transplantation.

Characteristic	Treated group ($n = 22$)	Serotype (no. with serotype)	Untreated group ($n = 13$)	Serotype (no. with serotype)
Median (range) day of first positive culture result[a]	44 (−5 to 184)		46 (13–120)	
Median (range) duration of positive cultures, days	21 (11–40)[b]		25 (10–60)[c]	
No. of sites of isolation				
1	14	1 (4), 2 (4), 3 (1), A31 (3), 5 (1)	11	1 (1)
2	3	1 (1), 2 (1), 8 (1)	2	A31 (1)
3	5	1 (1), 2 (2)	0	
Site of isolation				
Stool	22	1 (7), 2 (5), 3 (2), 5 (1), 8 (1), A31 (3)	12	2 (1), A31 (1)
Urinary tract	10	1 (4), 2 (2), 3 (1), 5 (1), 8 (1)	2	
Throat	3	1 (1), 8 (1), A31 (1)	0	
Lung	5	1 (1), 2 (1), 8 (1)	0	
Blood or bone marrow	2	1 (1), 2 (1)	0	
Liver	6	1 (3), 2 (1), 5 (1), A31 (1)	0	
CNS	5	1 (2), 2 (2)	1	
No. with pancytopenia[d]	16[e]	1 (5), 2 (4), 5 (1), 8 (1), A31 (3)	3	A31 (1)
No. with fever[d]	6	1 (4), 2 (1)	1	

[a] In relation to transplantation.
[b] Before onset of therapy.
[c] For 11 patients who spontaneously cleared adenovirus infection.
[d] Severe pancytopenia or high spiked fever concomitant with cultures positive for adenovirus.
[e] Includes 2 patients with graft failure.

Table 4. Outcomes among hematopoietic stem cell transplant (HSCT) recipients treated for adenovirus infections.

Type of infection, patient no.	HSCT type	Time of first culture positive for adenovirus, days after transplantation	Type of therapy		Outcome of adenovirus infection	Cause of death
			First-line, day of onset	Second-line/ third-line, day of onset		
Definite						
2	MUD	41	Ribavirin (42)		Persistent	Infection, GVHD
3	MUD	41	Ribavirin (63)		Persistent	Infection, GVHD
7	MUD	45	Ribavirin (46)	Vidarabine (62)	Persistent	Infection, graft failure
Probable						
6	MUD	35	Ribavirin + DLI (58)	Cidofovir (73)	Recovered	Alive
8	MMFM	43	Ribavirin + cidofovir (66)		Recovered	Alive
9	MUD	0	Ribavirin (49)	Vidarabine + cidofovir (60–79)/DLI (110)	Persistent	Infection
10	MS	64	Ribavirin (75)		Recovered	Alive
11	MUD	79	Ribavirin (105)		Persistent	Pneumonitis (CMV)
13	MUD	70	Ribavirin (138)		Persistent	Infection, GVHD
14	MUD	184	Ribavirin (193)	Ribavirin + vidarabine (360)	Recurrent[a]	Infection, GVHD
15	MUD	35	Ribavirin + vidarabine (46)		Persistent	Infection, graft failure
17	MUD	135	Ribavirin + vidarabine (143)		Persistent	Infection, GVHD
18	MUD	32	Ribavirin + DLI (41)	Ribavirin + DLI (55)	Recovered	Pneumonitis (idiopathic)
19	MS	50	Vidarabine (90)		Persistent	Infection, GVHD
Asymptomatic infection						
1	MS	64	Ribavirin (68)		Recovered	Alive
4	MUD	60	Ribavirin (74)		Recovered	Alive
5	MMFM	65	Ribavirin (83)		Persistent	Infection, GVHD
12	MUD	−5	Ribavirin (19–42)	Cidofovir (72)	Recurrent[a]	Infection
16	MUD	35	Ribavirin (62)	Vidarabine (75)	Recurrent[a]	Infection, GVHD
21	MMFM	48	Cidofovir (59)		Recovered	Alive
23	MUD	45	Cidofovir (81)		Recovered	Alive
Prophylactic, 22	MUD		Cidofovir (40)		Persistent	Infection, GVHD

NOTE. CMV, cytomegalovirus; DLI, donor leukocyte infusion; GVHD, graft-versus-host disease; MMFM, mismatched family member; MS, matched sibling; MUD, matched unrelated donor.

[a] After initial recovery.

differences in the probability of failure of antiviral therapy in relation to 2 factors: acute GVHD grade ≥ 3 ($P = .01$) and long delay between adenovirus infection and treatment ($P = .05$).

DISCUSSION

Adenovirus infections are emerging as an important cause of morbidity and mortality after allogeneic HSCT [1–7]. Indeed, 2%–21% of patients have been reported to develop significant adenovirus infection, resulting in an adenovirus-related mortality rate of 10%–60%, depending essentially on the level of the posttransplantation immunodeficiency. It was thought that the source of infection in most cases was endogenous virus reactivation as a result of posttransplant immunosuppression. Recently, as many as 65% of child recipients of unrelated HSCT have positive culture results for adenovirus at some time during their hospitalization [4]. The highest mortality rate, approaching 60%, occurs among recipients with invasive and/or disseminated disease [2]. Significant risk factors for developing invasive adenovirus disease are the presence of moderate to severe acute GVHD, use of steroids and other immunosuppressive agents, isolation of adenovirus from ≥ 2 sites, HLA-mismatched or unrelated transplants, and use of T cell–depleted bone marrow [1–7]. Moreover, pediatric patients appear to be infected by adenovirus more frequently and earlier than their adult counterparts [1, 4, 7].

Our data are comparable to those of other reports, with an overall incidence of 11.5% and a mortality rate of 41% (table

1). Our incidence of adenovirus disease (6.8%) is exactly the same as that in the Wisconsin study [4], with a comparable group of patients. Indeed, both of these studies included a large number of children who received T cell–depleted grafts from a matched unrelated donor or a mismatched family member. In addition, in our series, most of this high-risk population received pre- and/or posttransplant antithymocyte globulins.

Treatment of established adenovirus disease was disappointing. Various methods have been tried, such as high-dose IVIGs, ribavirin, or vidarabine [1, 4, 8–12, 16, 17]. However, the clinical efficacy of these agents remains unclear. Of the 50 reported patients who received ribavirin as first-line therapy, only 15 (30%) had clearance of adenovirus infection, mostly those with adenovirus-associated hemorrhagic cystitis (8 of 17) [12, 18–23]. High bladder concentrations could explain why ribavirin may have been effective for such patients. Our data are similar; indeed, only 4 (30.8%) of 13 patients who received ribavirin as the only first-line treatment recovered. One of them experienced reactivated adenovirus infection 5.5 months later and died, despite resumption of treatment with ribavirin combined with vidarabine. Two of 3 surviving patients received bone marrow from a matched sibling. Only 1 of 9 patients with definite or probable disease showed a clinical response to ribavirin therapy. We are uncertain whether the clearance of adenovirus was circumstantial. Indeed, 11 of 13 untreated patients spontaneously recovered. However, most of them received non–T cell-depleted bone marrow from matched siblings, had adenovirus isolated at a single site, and had no evidence of adenovirus disease. The most commonly reported adverse effect of ribavirin is reversible mild anemia induced by hemolysis. Such complications were not significant in our series.

Vidarabine is active in vitro against double-stranded DNA viruses, including human adenovirus. It has been reported to be effective in a few cases after HSCT, but only against hemorrhagic cystitis [10, 11]. Our results are appreciably different; indeed, our 7 treated patients showed no benefit from vidarabine, although only 1 had hemorrhagic cystitis.

Cidofovir is a nucleotide analogue of cytosine with potent in vitro activity against herpesviruses, polyomaviruses, and different serotypes of adenoviruses [24]. It recently has been shown to be a therapeutic option in life-threatening disseminated adenovirus diseases [13, 25, 26]. Indeed, of the 16 reported patients who received treatment, 9 (56%) responded. Five (71%) of our 7 treated patients had clearance of adenovirus; however, in 1 of them, infection promptly reactivated. These data should be interpreted with caution, because patients either received cidofovir combined with other treatments or had asymptomatic infections. These encouraging results were obtained at the expense of severe nephrotoxicity, as recently reported in ~15% of patients [27]. The close temporal relationship between the onset of renal failure, cidofovir administration, and the transient and partially reversible deterioration in renal function that occurred after each course strongly support the role of cidofovir in our observation.

Adenovirus-specific cellular immune responses, particularly long-lived adenovirus-specific $CD4^+$ T cells, have a major role in the prevention and control of viral infections [28]. Downregulation of the host immune response to adenovirus-infected cells facilitates the establishment of persistent and latent infections. Successful treatment of life-threatening adenovirus disease after HSCT with unmanipulated DLI was reported in 3 of 4 cases [1, 14, 17, 29]. The patients were given 1×10^6 to 1.9×10^7 $CD3^+$ cells/kg, with no evidence of GVHD, aplasia, or interstitial pneumonia. Similarly, DLI (dose range, $1–10 \times 10^5$ $CD3^+$ cells/kg, derived from matched unrelated donors) produced rapid clearance of virus in 2 of our 3 patients but at the expense of 1 case of fatal idiopathic respiratory failure. Indeed, although unmanipulated polyspecific donor T cells as treatment of Epstein-Barr virus–associated lymphoproliferative disorders are effective therapy, such treatments occasionally are complicated by GVHD and idiopathic interstitial pneumonia [30]. To circumvent these problems, several groups are exploring the use of viral antigen–specific cytotoxic T cells, which not only reconstitute host cellular immunity to Epstein-Barr virus or CMV, but also establish populations of cytotoxic T lymphocyte precursors that survive for a prolonged period and may respond to viral challenge [31, 32]. The other approach to reduce the risk of GVHD is to transduce T cells with a suicide gene, as evaluated by Bonini and colleagues [33]. Preclinical studies are underway to establish systems for generating adenovirus-specific cytotoxic T lymphocytes by using donor peripheral blood dendritic cells as antigen-presenting cells [34]. The extensive cross-reactivity of adenovirus-specific cytotoxic T cells suggests that adoptive transfer of cytotoxic T lymphocytes generated in vitro against a particular serotype could protect bone marrow recipients from infections of all serotypes [35].

In conclusion, ribavirin, vidarabine, and high-dose IVIGs are ineffective for patients who are at high risk for disseminated adenovirus disease. Conversely, cidofovir or adoptive immunotherapy seem to be encouraging approaches. Invasive adenovirus disease is associated with a very high risk of mortality. Therefore, it is imperative to treat adenovirus infection in a manner similar to that used for CMV infection, before it develops into disease. Two different approaches could be considered. In the first, preemptive therapy, patients are given cidofovir and/or DLI or adoptive transfer of specific cytotoxic T lymphocytes when adenovirus infections are first identified. In the second, prophylactic, approach, similar treatments are given to all patients who are at high risk of disseminated infection. Given the potential risk of such approaches, we have to better

define this high-risk subgroup of patients. Patients undergoing allogeneic transplantation complicated by moderate to severe acute GVHD with ⩾2 sites of infection are at the greatest risk of developing disseminated adenovirus disease. Among allogeneic recipients, there was a higher incidence of adenovirus disease in patients with unrelated or HLA-mismatched grafts than in patients with related HLA-matched grafts. In our series, a pediatric population, unrelated or mismatched related bone marrow, T cell–depleted BMTs, and prophylactic or curative antithymocyte globulins were significant high-risk factors (data not shown).

To accomplish this, we need more rapid and sensitive diagnostic approaches. Indeed, it takes several days or weeks to isolate adenoviruses from clinical specimens with culture-based diagnosis, whereas PCR analysis or in situ hybridization results are available within 24 h of testing [36, 37]. Further studies are needed to evaluate the sensitivity and clinical value of these techniques.

No significant factor is a definite indicator of which patients will respond to ribavirin therapy and which patients will not [1]. However, there is a trend toward better responses to ribavirin or vidarabine therapy among patients with isolated adenovirus-associated hemorrhagic cystitis, particularly for some recipients who receive transplants from a genetically close donor [23]. Moreover, Howard et al. [1] recently postulated that early preemptive therapy with ribavirin could prevent the development of adenovirus dissemination in high-risk patients. We agree with this strategy but not with the choice of the drug, which was ineffective in our experience.

In our study, 2 factors correlated significantly with an increased risk of treatment failure: acute GVHD grade ⩾3 and a long delay between first isolation of adenovirus and treatment. In conclusion, prospective trials are needed to determinate the efficacy of these different approaches for prevention and treatment of serious adenovirus disease in the context of hematopoietic stem cell transplantation.

References

1. Howard DS, Phillips II GL, Reece DE, et al. Adenovirus infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **1999**; 29: 1494–501.
2. Blanke C, Clark C, Broun R, et al. Evolving pathogens in allogeneic bone marrow transplantation: increased fatal adenoviral infections. Am J Med **1995**; 99:326–8.
3. Shields AF, Hackman RC, Fife KH, et al. Adenovirus infections in patients undergoing bone marrow transplantation. N Engl J Med **1985**; 312:529–33.
4. Flomenberg P, Babbit J, Drobyski WR, et al. Increasing incidence of adenovirus disease in bone marrow transplant recipients. J Infect Dis **1994**; 169:775–81.
5. Munoz FM, Piedra PA, Demmler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. Clin Infect Dis **1998**; 27:1194–200.
6. Bruno B, Boeckh M, Davis C, et al. Adenovirus infections in patients undergoing bone marrow transplantation. In: Program and abstracts of the 39th meeting of the American Society of Hematology (San Diego). **1997**:1867a.
7. Hale GA, Heslop HE, Krance RA, et al. Adenovirus infection after pediatric bone marrow transplantation. Bone Marrow Transplant **1999**; 23:277–82.
8. La Rosa A, Champlin R, Rolston K, et al. Adenovirus infections in adult bone marrow transplant recipients [abstract 289]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for Microbiology, **1999**:423.
9. Hromas R, Clark C, Blanke C, et al. Failure of ribavirin to clear adenovirus infections in T cell–depleted allogeneic bone marrow transplantation. Bone Marrow Transplant **1994**; 14:663–6.
10. Kawakami M, Ueda S, Maeda T, et al. Vidarabine therapy for virus-associated cystitis after allogeneic bone marrow transplantation. Bone Marrow Transplant **1997**; 20:485–90.
11. Kitabayashi A, Hirokawa M, Kuroki J, et al. Successful vidarabine therapy for adenovirus type 11–associated acute hemorrhagic cystitis after allogeneic bone marrow transplantation. Bone Marrow Transplant **1994**; 14:853–4.
12. Murphy GF, Wood DP, McRoberts JW, Henslee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. J Urol **1993**; 149:565–6.
13. Ribaud P, Scieux C, Freymuth F, et al. Successful treatment of adenovirus disease with intravenous cidofovir in an unrelated stem-cell transplant recipient. Clin Infect Dis **1999**; 28:690–1.
14. Hromas R, Cornetta K, Srour E, et al. Donor leukocyte infusion as therapy of life-threatening adenoviral infections after T-cell–depleted bone marrow transplantation. Blood **1994**; 84:1689–90.
15. Venard V, Carret AS, Corsaro D, et al. Genotyping of adenoviruses isolated in an outbreak in a bone marrow transplant unit shows that diverse strains are involved. J Hosp Infect **2000**; 44:71–4.
16. Kapelushnik J, Or R, Delukina M, et al. Intravenous ribavirin therapy for adenovirus gastroenteritis after bone marrow transplantation. J Pediatr Gastroenterol Nutr **1995**; 21:110–2.
17. Chakrabarti S, Collingham KE, Fegan CD, Milligan DW. Fulminant adenovirus hepatitis following unrelated bone marrow transplantation: failure of intravenous ribavirin therapy. Bone Marrow Transplant **1999**; 23:1209–11.
18. Cassano WF. Intravenous ribavirin therapy for adenovirus cystitis after allogeneic bone marrow transplantation. Bone Marrow Transplant **1991**; 7:247–8.
19. Liles WC, Cushing H, Holt S, et al. Severe adenoviral nephritis following bone marrow transplantation: successful treatment with intravenous ribavirin. Bone Marrow Transplant **1993**; 12:409–12.
20. Jurado M, Navarro JM, Hernandez J, et al. Adenovirus-associated haemorrhagic cystitis after bone marrow transplantation successfully treated with intravenous ribavirin. Bone Marrow Transplant **1995**; 15: 651–2.
21. Londergan TA, Walzak MP. Hemorrhagic cystitis due to adenovirus infection following bone marrow transplantation. J Urol **1994**; 151: 1013–4.
22. Mann D, Moreb J, Smith S, Gian V. Failure of intravenous ribavirin in the treatment of invasive adenovirus infection following allogeneic bone marrow transplantation: a case report. J Infect **1998**; 36:227–8.
23. Miyamura K, Hamaguchi M, Taji H, et al. Successful ribavirin therapy for severe adenovirus hemorrhagic cystitis after allogeneic marrow transplant from HLA donors rather than distant donors. Bone Marrow Transplant **2000**; 25:545–8.
24. Romanowski EG, Gordon YJ. Efficacy of topical cidofovir on multiple adenoviral serotypes in the New Zealand rabbit ocular model. Invest Ophthalmol Vis Sci **2000**; 41:460–3.
25. Izadifar-Legrand F, Berrebi D, Faye A, et al. Early diagnosis of adenovirus infection and treatment with cidofovir after bone marrow transplantation in children [abstract 1526]. In: Program and abstracts

of the 41st meeting of the American Society of Hematology (New Orleans). W. B. Saunders Company, Philadelphia, **1999**:343a.
26. Ljungman P, Lambertenghi Deliliers G, Ribaud P, et al. Cidofovir for treatment of CMV and adenovirus infections in allogeneic stem cell transplant recipients [abstract 1753]. In: Program and abstracts of the 41st meeting of the American Society of Hematology (New Orleans). W. B. Saunders Company, Philadelphia, **1999**:396a.
27. Vandercam B, Moreau M, Goffin E, et al. Cidofovir-induced end-stage renal failure. Clin Infect Dis **1999**; 29:948–9.
28. Flomenberg P, Piaskowski V, Truitt RL, Casper JT. Characterization of human proliferative T cell responses to adenovirus. J Infect Dis **1995**; 171:1090–6.
29. Miyamoto T, Gondo H, Miyoshi Y, et al. Early viral complications following CD34-selected autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Br J Haematol **1998**; 100:348–50.
30. Papadopoulos EB, Ladanyi M, Emanuel D, et al. Infusions of donor leukocytes to treat Epstein-Barr virus–associated lymphoproliferative disorders after allogeneic bone marrow transplantation. N Engl J Med **1994**; 330:1185–91.
31. Sun Q, Pollok KE, Burton RL, et al. Simultaneous ex vivo expansion of cytomegalovirus and Epstein-Barr virus–specific cytotoxic T lymphocytes using B-lymphoblastoid cell lines expressing cytomegalovirus pp65. Blood **1999**; 94:3242–50.
32. Rooney CM, Smith CA, Ng CYC, et al. Infusion of cytotoxic T cells for the prevention and treatment of Epstein-Barr virus–induced lymphoma in allogeneic transplant recipients. Blood **1998**; 92:1549–55.
33. Bonini C, Ferrari G, Verzeletti S, et al. HSV-TK gene transfer into donor lymphocytes for control of allogeneic graft versus leukemia. Science **1997**; 276:1719–24.
34. Smith CA, Woodruff LS, Kitchingman GR, Rooney CM. Adenovirus-pulsed dendritic cells stimulate human virus–specific T-cell responses in vitro. J Virol **1996**; 70:6733–40.
35. Smith CA, Woodruff LS, Rooney CM, Kitchingman GR. Extensive cross-reactivity of adenovirus-specific cytotoxic T cells. Hum Gene Ther **1998**; 9:1419–27.
36. Echavarria MS, Ray SC, Ambinder R, et al. PCR detection of adenovirus in a bone marrow transplant recipient: hemorrhagic cystitis as a presenting manifestation of disseminated disease. J Clin Microbiol **1999**; 37:686–9.
37. Matsuse T, Matsui H, Shu CY, et al. Adenovirus pulmonary infections identified by PCR and in situ hybridisation in bone marrow transplant recipients. J Clin Pathol **1994**; 47:973–7.