Biol Blood Marrow Transplant 20 (2014) 250–256

Patient, Virus, and Treatment-Related Risk Factors in Pediatric Adenovirus Infection after Stem Cell Transplantation: Results of a Routine Monitoring Program

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Article history:
Received 4 September 2013
Accepted 12 November 2013

Key Words:
Human adenovirus
Stem cell transplantation
Pediatric transplantation
Surveillance strategy

A B S T R A C T

Human adenovirus (HAdV) infection after hematopoietic stem cell transplantation (HSCT) is associated with significant morbidity and mortality in children. The optimal surveillance and treatment strategies are under discussion. Here, we present data from 238 consecutive pediatric allogeneic HSCT recipients who underwent transplantation in a single center who were included in a prospective, weekly HAdV DNAemia monitoring program by quantitative PCR. HAdV loads >1000 copies/mL were detected in 15.5% of all patients. Despite a low mortality directly attributed to HAdV infection (2 patients, 0.84%), blood HAdV loads >10,000 copies/mL (6.7% of all patients) were significant and independent risk factors for poor survival. We searched for patient, virus, and treatment-related risk factors of HAdV DNAemia and disease. Detection of HAdV in blood before day 50 post transplantation was a major independent risk factor for the development of blood HAdV loads >10,000 copies/mL. HAdV typing revealed A31, C1, and C2 as the predominant pathogens among several other HAdV strains with type C species detected in most patients with severe HAdV disease. Stool HAdV loads were prospectively monitored in 111 patients and correlated with but did not significantly precede detection in blood. Treatment with cidofovir led to stable or reduced viral load in 70% of patients with blood HAdV loads >1000 copies/mL. Thus, early occurrence of HAdV-DNA in blood of pediatric HSCT recipients predisposes for development of high viral loads. Control of HAdV infections was attempted by preemptive cidofovir treatment of patients with high blood HAdV loads or with symptomatic organ infections and correlated with low HAdV-attributed mortality.

INTRODUCTION

Human adenovirus (HAdV) infections are serious complications of pediatric allogeneic hematopoietic stem cell transplantation (HSCT) with up to 5% of pediatric HSCT patients succumbing to these infections [1–3]. Severe, disseminated HAdV infections are lethal in up to 100% [4]. Risk factors for HAdV infection are controversial but include donor type [1], conditioning regimen [5], and T cell depletion [6–9]. Monitoring for HAdV is recommended for pediatric patients after HSCT [7] and quantitative HAdV polymerase chain reaction (PCR) from peripheral blood, stool, and other material is considered reliable, sensitive, and expeditious [2]. The incidence of HAdV detection by PCR in peripheral blood of pediatric HSCT patients varies between 8% and 21% [4,10–12] and high blood HAdV loads are a risk factor for disseminated HAdV disease [13]. Although several HAdV outbreaks have been reported in pediatric HSCT units [14,15], HAdV infections during HSCT-related immunosuppression are mainly reactivations from asymptomatic HAdV persistence in the upper respiratory tract [16], intestine [4], and/or urinary tract [17].

Treatment options for HAdV infections are currently not satisfying. Cidofovir is state-of-the-art for both preemptive and therapeutic treatment of HAdV infections [7,11,18], despite relevant toxicities [11,19]. Even with antiviral treatment, clearance of HAdV is closely related to immune reconstitution after HSCT [20]; therefore, withdrawal of immunosuppression is advocated where possible [8]. The use of HAdV-specific donor-derived T cells offers an additional therapeutic approach [21]. Instead of ex vivo amplified HAdV-specific T cells, unmanipulated donor lymphocyte infusions have been used with acceptable side effects, even in haploidentical transplantations [22].

Identification of patients at high risk for severe HAdV disease is crucial to stratify patients to pre-emptive treatment. To date, risk factor analysis is hampered by the difficulty in comparing results of monitoring methods (mostly PCR-based) between different transplantation centers and laboratories. Therefore, large, single-center studies are currently the most feasible way to approach this problem.

Here, we evaluate results of prospective quantitative HAdV-PCR monitoring, HAdV disease, and treatment outcome in 238 consecutive pediatric HSCT recipients who

Financial disclosure: See Acknowledgments on page 255.

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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.11.009

underwent transplantation at our institution over a 9-year period. We show that the magnitude of peak HAdV blood loads correlates with overall transplantation outcome. Therefore, we aim to identify the characteristics of patients who will most likely benefit from antiviral treatment. We identify risk factors for the development of high peak HAdV blood loads, and evaluate the course of antiviral treatment with cidofovir.

PATIENTS, MATERIALS, AND METHODS

Study Concept and Data Source

This retrospective analysis was approved by the institutional review board of Hannover Medical School. All consecutive patients undergoing first HSCT between January 1, 2003, and February 28, 2012, at our center were included. Data on HAdV infection of 6 patients were previously reported [15]. Quantitative HAdV PCR results were collected prospectively. Real-time PCR assays and HAdV typing were performed by the German National Reference Laboratory for Adenoviruses, Hannover Medical School. Clinical data was retrieved from the pediatric HSCT database and medical records.

Patient Characteristics

A total of 238 consecutive pediatric allogeneic HSCT patients were included. Median follow-up was 24 months (range, 1 to 105) for the surviving patients. Patient characteristics are displayed in Table 1. Patients underwent transplantation for both malignant (n = 130) and nonmalignant disease (n = 108). The majority (89%) underwent transplantation from matched donors, whereas 25 patients received alternative stem cell grafts (18 mismatched related donor grafts, 3 mismatched unrelated donor grafts, and 4 cord blood grafts). Fifteen patients (6.3%) received a second HSCT.

Definitions

The cause of death was defined following the algorithm developed by Copelan and colleagues [23]. A death that was classified as caused by infection and that occurred after detection of any HAdV in a vital organ (lung, liver, cerebrospinal fluid) or blood (load >1000 copies/mL) within the last 30 days before death was classified as HAdV-related. HAdV disease was defined as symptomatic disease with concomitant detection of HAdV at the site of infection or in blood.

HAdV Monitoring

Routine quantitative HAdV-PCR monitoring from peripheral blood was performed weekly from the time of admission until discharge and monthly thereafter until day +180. A median of 18 (range, 1 to 66) samples per patient have been evaluated. After July 2008, routine quantitative HAdV-PCR monitoring from stool was performed once weekly until discharge, and thereafter whenever clinically indicated. A median of 5 samples (range, 0 to 41) per patient were tested. Before July 2008, stool HAdV-PCR was performed only upon clinical indication.

Quantitative real-time HAdV-PCR and molecular typing were performed as previously described [24–26]. Contamination was monitored by adequate negative controls. The lower quantification limit of the quantitative PCR

Table 1
Patient Characteristics and Peak Blood HAdV Load

Characteristic	n	%	Peak Blood HAdV Load				*P* Value
			Negative	Less than 1000 Copies/mL	1000 to 10,000 Copies/mL	More than 10,000 Copies/mL	
Sex							.377
Male	138	58%	75	43	11	9	
Female	100	42%	43	40	10	7	
Age							.065
<6 yr	90	38%	36	34	11	9	
≥6 yr	148	62%	82	49	10	7	
Underlying disease							.564
Acute leukemia	98	41%	40	34	8	10	
Chronic leukemia	9	4%	4	3	2		
Solid tumors	3	1%	2	1			
Lymphoma	6	3%	4	1	1		
MDS	14	6%	11	5	1		
SAA	13	5%	7	6			
Hemoglobinopathies	23	10%	14	6	3		
Inborn errors of hematopoiesis	23	10%	14	8	3	1	
Inborn errors of metabolism	12	5%	8	2	1	1	
Immunodeficiency syndrome/HLH	37	16%	14	17	2	4	
Conditioning regimen							.413
Treosulfan-based	73	31%	37	22	6	8	
Busulfan-based	65	27%	31	22	9	3	
TBI-based	65	27%	30	26	4	5	
Other	35	15%	20	13	2		
T cell depletion							.641
No T cell depletion	36	15%	19	14	3		
ATG/ALG	125	53%	66	40	10	9	
alemtuzumab	39	16%	16	16	3	4	
OKT3	4	2%	1	2		1	
In vitro T cell depletion	34	14%	16	11	5	2	
Stem cell source							.458
MRD	77	32%	41	27	8	1	
MUD	136	57%	65	47	11	13	
Alternative donor	25	11%	12	9	2	2	
Acute GvHD							.248
No aGvHD	124	52%	66	43	7	8	
aGvHD I°	47	20%	24	15	7	1	
aGvHD ≥ II°	67	28%	28	25	7	7	
Chronic GvHD							.143
No	214	90%	109	70	19	16	
Yes	24	10%	9	13	2		

ATG/ALT indicates Anti-thymocyte globulin or anti-lymphocyte globulin; HAdVs, human adenovirus; GvHD, graft-versus-host disease; aGvHD, acute GvHD; MDS, myelodysplastic syndrome; MRD, matched related donor; MUD, matched unrelated donor; SAA, severe acute anemia; TBI, total body irradiation.
P values indicate results of Pearson's chi-square test.