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Risk Factors and Utility of a Risk-Based Algorithm for Monitoring Cytomegalovirus, Epstein-Barr Virus, and Adenovirus Infections in Pediatric Recipients after Allogeneic Hematopoietic Cell Transplantation

Evelyn Rustia [1], Leah Violago [2], Zhezhen Jin [3], Marc D. Foca [1], Justine M. Kahn [1], Staci Arnold [4], Jean Sosna [1], Monica Bhatia [1], Andrew L. Kung [1], Diane George [1], James H. Garvin [1], Prakash Satwani [1,*]

[1] *Department of Pediatrics, Columbia University Medical Center, New York, New York*
[2] *Department of Nursing, New York-Presbyterian Morgan Stanley Children's Hospital, New York, New York*
[3] *Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York*
[4] *Department of Pediatrics, Emory University, Atlanta, Georgia*

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A B S T R A C T

Infectious complications, particularly viral infections, remain a significant cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (alloHCT). Only a handful of studies in children have analyzed the risks for and impact of viremia on alloHCT-related outcomes. We conducted a retrospective study of 140 pediatric patients undergoing alloHCT to investigate the incidence of and risk factors for cytomegalovirus (CMV), adenovirus (ADV), and Epstein-Barr virus (EBV) viremia and viral disease after alloHCT. Furthermore, we assessed the impact of viremia on days of hospitalization and develop an algorithm for routine monitoring of viremia. Patients were monitored before alloHCT and then weekly for 180 days after alloHCT. Patients were considered to have viremia if CMV were > 600 copies/mL, EBV were > 1000 copies/mL, or ADV were > 1000 copies/mL on 2 consecutive PCRs. The overall incidences of viremia and viral disease in all patients from day 0 to +180 after alloHCT were 41.4% (n = 58) and 17% (n = 24), respectively. The overall survival for patients with viremia and viral disease was significantly lower compared with those without viremia (58% versus 74.2%, $P = .03$) and viral disease (48.2% versus 71.2%, $P = .024$). We identified that pre-transplantation CMV risk status, pre-alloHCT viremia, and use of alemtuzumab were associated with the risk of post-alloHCT viremia. The average hospitalization days in patients with CMV risk ($P = .011$), viremia ($P = .024$), and viral disease ($P = .002$) were significantly higher. The algorithm developed from our data can potentially reduce viral PCR testing by 50% and is being studied prospectively at our center. Improved preventative treatment strategies for children at risk of viremia after alloHCT are needed.

INTRODUCTION

Over the past 4 decades, allogeneic (allo) hematopoietic cell transplantation (HCT) has provided a curative treatment option for pediatric patients with both malignant and nonmalignant diseases [1,2]. In alloHCT recipients, advances in methods of donor selection, graft-versus-host disease (GVHD) management, and molecular monitoring for infectious organisms have resulted in improved overall survival (OS) [3-7]. Despite these advances, infectious complications, particularly viral infections, remain a significant cause of morbidity and mortality after alloHCT. Because of a period of prolonged immune suppression after alloHCT, patients undergoing alloHCT are at high risk for infection with cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus (ADV) [8].

After alloHCT, early treatment with antiviral medications in a patient with rising viral copies has reduced the risk of morbidity and mortality associated with viral infections, most notably, with CMV [7,9,10]. Although pre-

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* Correspondence and reprint requests: Prakash Satwani, MD, Associate Professor of Pediatrics, Division of Pediatric Blood and Bone Marrow Transplantation, New York-Presbyterian Morgan Stanley Children's Hospital, Columbia University, 3959 Broadway, CHN 10-04, New York, NY 10032.
E-mail address: ps2087@columbia.edu (P. Satwani).

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Table 1
Patient Demographics and Transplantation Characteristics (n = 140)

Characteristic	Value
Age at transplantation, mean ± SD (range), yr	9.46 ± 6.09 (.25-22)
Female	55 (39.3%)
Malignant disease	69 (49.3%)
Matched related donor	57 (40.7%)
Stem cell source	
Cord blood	22 (15.7%)
Peripheral blood stem cells	40 (28.6%)
Bone marrow	78 (55.7%)
Conditioning regimen	
MAC	58 (41.4%)
RTC	53 (37.9%)
RIC	29 (20.7%)
Serotherapy	
Alemtuzumab	75 (53.6%)
r-ATG	40 (28.6%)
Neither r-ATG nor alemtuzumab	25 (17.9%)

MAC indicates myeloablative conditioning; RTC, reduced-toxicity conditioning; RIC, reduced-intensity conditioning.
Data presented are n (%), unless otherwise indicated.

emptive treatment with i.v. ganciclovir has been shown to decrease the cumulative incidence of CMV disease [11,12], pre-emptive treatment of ADV and EBV is not well established [13]. There are currently no well-established guidelines for the frequency of viral monitoring in children after alloHCT. Only a handful of studies in children have analyzed the risks for and impact of viremia on alloHCT-related outcomes [8,14]. Pretransplantation CMV serostatus is an important risk factor for the development of CMV viremia. In patients who are seropositive before transplantation, the incidence of CMV viremia approaches 70% [15].

Ex vivo T cell depletion and T cell–depleting agents such as alemtuzumab or antithymocyte globulin (ATG) are used for the prevention of GVHD and graft rejection but carry an increased risk of viral infection because of the resultant delay in immune reconstitution [16,17].

We conducted a retrospective study of pediatric patients undergoing alloHCT to investigate the incidence of and risk factors for viremia and viral disease (CMV, ADV, and EBV) after transplantation. Furthermore, we assessed the impact of viremia on length of hospitalization and used the gathered data to develop an algorithm for routine monitoring of viremia for first 6 months in pediatric patients undergoing alloHCT.

METHODS

Patients

This was a retrospective study of 140 pediatric patients who received alloHCT for malignant and nonmalignant diseases at the Columbia University Medical Center. Patients underwent transplantation between 2008 and 2014. For this analysis, eligible patients were identified from a transplantation database and clinical data were collected from the electronic medical record. This study was approved by the institutional review board of the Columbia University Medical Center.

Conditioning Regimens

The myeloablative conditioning regimen consisted of either total body irradiation (12 Gray) plus 1 or 2 high-dose alkylators or busulfan (12.8 mg/kg-16 mg/kg) plus 1 high-dose alkylator. Reduced-toxicity regimens consisted of busulfan (12.8 mg/kg-16 mg/kg) or cyclophosphamide (200 mg/kg) plus fludarabine. Reduced-intensity regimens contained busulfan (6.4 mg/kg-8 mg/kg) or melphalan (140 mg/m^2) plus fludarabine. Serotherapy consisted of alemtuzumab (54 mg/m^2) or ATG (8 mg/kg) [3].

GVHD Prophylaxis and Grading

Acute GVHD (aGVHD) prophylaxis in the majority of patients consisted of tacrolimus and mycophenolate mofetil, as previously described [18,19]. Tacrolimus and/or mycophenolate mofetil were tapered if patients had ≤grade II aGVHD on day +30 for those with malignant diseases and on day +180 for those with nonmalignant diseases [18,19]. Grading of aGVHD was per established criteria by Glucksberg et al. [20].

Post-alloHCT Viral Prophylaxis

Patients at risk for CMV received acyclovir prophylaxis, which was continued until the following criteria were met: absolute neutrophil count (ANC) > .75 × 10^9/L × 2 days and < grade II mucositis. When these criteria were met, patients were transitioned to ganciclovir/foscarnet or valganciclovir daily until day +100, as previously published [21].

Viral Monitoring and Treatment of Viremia

In 2008, our center created a standard operating procedure for prospective quantitative PCR monitoring for CMV, EBV, and ADV. Patients were monitored at least once within 4 weeks before the start of conditioning regimen and then weekly for 180 days after alloHCT. CMV PCR was performed in house as per protocol established by Roche Diagnostic (Indianapolis, IN) and EBV and ADV PCR were performed by Viracor (Lee, Summit, MO). Patients with a positive CMV PCR after HCT were treated with induction ganciclovir for 2 weeks (or until PCR negative), followed by maintenance ganciclovir or foscarnet for at least 4 weeks. Foscarnet was administered in a few patients with severe neutropenia and a few patients with increasing CMV copy number on ganciclovir treatment. Foscarnet was started at 90 mg/kg twice a day and the dose was adjusted based on creatinine clearance. Patients with ADV viremia were treated with cidofovir (5 mg/kg/dose once a week). When the viral copy number started to decline by a log, cidofovir was administered every 2 weeks. The dose and duration of cidofovir were titrated based on renal functions and viral load. Those with EBV viremia received rituximab (375 mg/m^2) for 2 to 4 weeks and were tapered off immune suppression as tolerated.

Definitions

CMV risk

Patients were considered to have a *positive CMV risk status* if either donor or recipient or both were CMV IgG positive before transplantation.

Viremia

Patients were considered to have *viremia* if CMV, EBV, ADV copies/mL were > 600, > 1000, and > 1000, respectively, on 2 consecutive PCRs. The cutoff for positivity for EBV and ADV were PCR levels above these thresholds of detection. This was similar to cutoffs used in published studies [16,22]. Post-transplantation viremia was defined as *very early* (day 0-14), *early* viremia (day 15-98), and *late* viremia (day 99-180). Resolution of viremia was defined as negative PCR testing for ≥ 2 weeks.

Viral disease

Definitions for CMV disease and ADV disease are those as previously described by Ljungman et al. [23-25]. A diagnosis of CMV/EBV/ADV disease required the presence of signs or symptoms of viral disease and radiological findings suggestive of viral infection along with 1 of the following: (1) detection of CMV/EBV/ADV in bronchoalveolar fluid, cerebrospinal fluid, or urine or tissue samples such as lung, gastrointestinal, liver, or lymph node

Table 2
Kinetics of Onset of Viremia Based on Use of Serotherapy and CMV Risk Status

Variable	n	CMV		ADV		EBV		Total
		Day 0-99	Day 100-180 (New Onset)	Day 0-99	Day 100-180 (New Onset)	Day 0-99	Day 100-180 (New Onset)	
Alemtuzumab	75	23	0	10	0	4	1	38
r-ATG	40	6	0	3	0	6	2	17
No serotherapy	25	2	0	2	0	1	0	5
CMV −/−	55	0	0	5	0	8	2	15