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Brief Articles

African American Race Is a Newly Identified Risk Factor for Postengraftment Blood Stream Infections in Pediatric Allogeneic Blood and Marrow Transplantation

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A B S T R A C T

Blood stream infections (BSI) are a major source of morbidity and mortality both in allogeneic blood and marrow transplant (BMT) recipients. Various risk factors for BSI in BMT have been identified. The impact of race and cytomegalovirus (CMV) viremia, a common complication after engraftment, however, has not been rigorously assessed. This is important because both CMV infection and ganciclovir, the mainstay of pre-emptive therapy, have myelosuppressive and immunosuppressive effects. We conducted a retrospective analysis to test the hypothesis that race and CMV viremia predispose allogeneic BMT patients to postengraftment BSI. We analyzed 278 allogeneic BMT performed at Children's Healthcare of Atlanta between January 1, 2005 and December 31, 2014 that met eligibility criteria. We performed a multivariate analysis to estimate the effect of CMV viremia on risk for BSI in the postengraftment period (days +30 to 100). Risk for BSI was associated with CMV viremia (hazard ratio [HR], 3.34; 95% confidence interval [CI], 1.51 to 7.36; $P = .003$); grade III and IV acute graft-versus-host disease (HR, 3.28; 95% CI, 1.55 to 6.92; $P = .002$), and African American race (HR, 2.22; 95% CI, 1.09 to 4.51; $P = .027$). The results of our study highlight the importance of a novel risk factor for postengraftment BSI, not previously considered—African American race.

INTRODUCTION

Blood stream infection (BSI) is a common source of morbidity and mortality in blood and marrow transplantation (BMT) [1-5]. A variety of risk factors for BSI in this setting have been implicated, including mucositis, donor type, and acute graft-versus-host disease (GVHD)[1-12]. To date, race has not previously recognized as a risk for BSI in this clinical setting; however, several studies performed in other setting have shown patients of African descent to be at increased risk for bacteremia and sepsis [13-17]. Meanwhile, the influence of cytomegalovirus (CMV) reactivation, a complication common during the second and third months after transplantation [18], on risk for BSI has not been rigorously explored. This is important because both CMV infection and ganciclovir (GCV), the mainstay of pre-emptive therapy, have myelosuppressive and immunosuppressive effects [19-24]. We retrospectively assessed the risk for bacterial BSI from African American race or CMV viremia in children and adolescents who received allogeneic BMT at our center over a 10-year period.

PATIENTS AND METHODS

Eligibility

We retrospectively collected data on allogeneic transplantations at Aflac Cancer and Blood Disorders Center, Emory University and Children's Healthcare of Atlanta between January 1, 2005 and December 31, 2014. We identified 329 allogeneic transplantations, in 301 patients, that were potentially eligible. We excluded 51 transplantations for the following reasons: death or leukemic relapse before day +30, neutrophil recovery occurring after day +30, transplantation occurred in the absence of conditioning, secondary graft failure between day +30 and +100, prophylaxis against CMV was administered, the patient had CMV viremia before transplantation, or the patient's BSI was diagnosed during an outbreak cluster of bacteremias that occurred in our institution in September 2007, which could have potentially confounded results from that period. Two hundred seventy-eight transplantations met criteria for inclusion. Their clinical features are shown in Table 1. Clinical data were abstracted from the medical records. The primary outcome was the first episode of BSI occurring between day +30 and +100 after allogeneic BMT. We compared clinical characteristics between patients with and without BSI between day +30 and +100 after allogeneic BMT.

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Table 1
Transplantation-Related Characteristics of Recipients in Postengraftment Period after Allogeneic BMT

Characteristic	Total (N = 278)	African American (n = 108)	Other than African American (n = 170)
Age, range (median), yr	0-22 (9)	0-20 (9)	0-22 (9)
Sex			
Female	115	47	68
Male	163	61	102
BMT period			
2005-2009	127	47	80
2010-2014	151	61	90
Donor			
Matched related BM/PBSC/CB	112	48	64
Mismatched related BM/PBSC	19	9	10
Unrelated BM/PBSC	71	17	54
Unrelated CB	76	34	42
Conditioning			
Myeloablative conditioning	221	87	134
Reduced-intensity conditioning	57	21	36
GVHD prophylaxis			
CSA + sMTX	153	52	101
CSA + MMF	75	28	48
CSA + mPSL	12	9	3
Others	38	20	18
Underlying disease			
Malignant diseases	165	52	113
Acute lymphoblastic leukemia	66	22	44
Acute myeloid leukemia	64	24	40
MDS/JMML/CMML	17	4	13
MPAL/undifferentiated	9	2	7
Peripheral T cell lymphoma	3	1	2
Lymphoblastic lymphoma	2	0	2
Diffuse large B cell lymphoma	2	0	2
Hodgkin lymphoma	2	0	2
Nonmalignant diseases	90	42	48
Sickle cell disease	32	31	1
Severe aplastic anemia	17	4	13
Hemophagocytic lymphohistiocytosis	12	3	9
Beta-thalassemia	7	0	7
Fanconi anemia	6	1	5
Mucopolysaccharidosis type I	4	1	3
Diamond-Blackfan anemia	3	1	2
Paroxysmal nocturnal hemoglobinuria	3	0	3
Dyskeratosis congenita	2	0	2
Langerhans cell histiocytosis	2	1	1
Glanzmann thrombasthenia	1	0	1
Metachromatic leukodystrophy	1	0	1
Immunodeficiencies	23	13	10
Severe combined immunodeficiency	5	3	2
Chronic granulomatous disease	5	2	3
Wiskott-Aldrich syndrome	4	3	1
Leukocyte adhesion deficiency	3	3	0
Omen syndrome	2	1	1
Shwachman-Diamond syndrome	2	0	2
Common variable immune deficiency			
Severe congenital neutropenia	1	0	1

BM indicates bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; CSA, cyclosporine; MTX, methotrexate; MMF, mycophenolate mofetil; mPSL, methylprednisolone; MDS, myelodysplastic syndrome; JMML, juvenile myelomonocytic leukemia; CMML, chronic myelomonocytic leukemia; MPAL, mixed phenotype acute leukemia.

Definitions

BSI was diagnosed if 1 or more blood cultures were positive for a bacterial pathogen. Two or more positive blood cultures were required (at least 2 times within 72 hours and/or 2 different sites) to meet the definition of a BSI for the following organisms: *Propionibacterium spp.*, *Bacillus spp.*, Coagulase negative staphylococci, *Clostridium perfringens*, and viridans group streptococci. Those organisms are more often associated with contamination, sometimes to rates as high as 30% [25-28].

Blood cultures were obtained in response to a sign of infection, typically fever. *Fever* was defined in this study as an oral temperature >38.5°C or 2 consecutive readings of >38.0°C for 2 hours. *Date of engraftment* was defined as the beginning day of at least 3 consecutive days of an absolute neutrophil count of $> .5 \times 10^9$/L after BMT. Monitoring of CMV viremia was performed weekly; however, it was not regularly screened in transplantations where both recipient and donor were seronegative because a primary infection was rare and likely to be symptomatic, prompting a workup for CMV infection. All cord blood units were considered seronegative. Monitoring was initiated by the fourth week after transplantation, using a quantitative, plasma-based PCR assay and continued through day +100. *CMV viremia* was defined as a single test demonstrating ≥300 copies/mL (level of detection). CMV viremia was treated with i.v. GCV (5 mg/kg/dose every 12 hours) or oral valganciclovir (VGCV) (15 mg/kg/dose (maximum 900 mg) every 12 hours). Herpes simplex virus–seropositive patients received acyclovir prophylaxis (250 mg/m^2 i.v. every 8 hours) starting on day -1 and typically discontinued just before initial discharge.

All patients were classified by race as African American or others according to the National Institute of Health/Office for Human Research Protections definition [29].

Data were analyzed as of January 31, 2016. The Children's Healthcare of Atlanta institutional review board approved this project, and a waiver of informed consent was obtained.

Statistical Analysis

This analysis was based on a time-dependent competing risk model. Risk events including acute GVHD (aGVHD) and CMV viremia were counted only when they preceded the BSI. Patients who relapsed/died within day +100 were censored at the time of relapse/death. Patients with multiple BSIs were also censored after their first episode of BSI. Medicaid or no insurance was examined to evaluate socio economic status of the patients.

A chi-square test or Mann-Whitney U test was used to compare patients with or without BSI. Risk factors for BSI were evaluated by univariate and multivariate analyses using the Cox regression model. A multivariate model was constructed by the backward stepwise method using threshold *P* values of .10 for removal or additions to the model. Values of $P < .05$ were considered significant. Measures of association are expressed as hazard ratios (HR) with a 95% confidence interval (CI). All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics [30].

RESULTS

Incidence and Causes of BSI

The cumulative incidence of BSI between day +30 and +100 was 21.9% (95% CI, 17.5% to 27.3%). The median day of BSI development was 54 (range, 30 to 99). Organisms causing BSI in this period are shown in Table 2. The leading cause was *Staphylococcus epidermidis*. Three cases with *Staphylococcus epidermidis* and 1 with *Clostridium perfringens* were not classified as cases with BSI because they had only a single positive blood culture. Collectively, gram-positive cocci were responsible for 71.4% of BSIs. In patients with gut (stage 1 to 4) GVHD, 11 (44%) of 25 BSIs were caused by bacteria other than staphylococci; in patients without gut GVHD 21 (55.3%) of 38 BSIs were caused by bacteria other than staphylococci.

Risk Factors

Baseline patient, disease, and transplantation characteristics, categorized by whether recipients developed BSI, and the results of univariate analysis, are shown in Table 3. BSIs were associated with African American race, grade III or IV aGVHD, and CMV viremia. Donor-recipient CMV serostatus and form of insurance (Medicaid/no insurance versus other) had no bearing on risk. There was no correlation between the frequency of CMV viremia and race (African American, 21.3%; others, 20.0%; $P = .879$). Because the majority of patients with CMV viremia received GCV/VGCV, we could not evaluate the independent impact of GCV/VGCV treatment. Sickle cell disease was not associated with BSI.