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Vancomycin-Resistant *Enterococcus* Colonization and Bacteremia and Hematopoietic Stem Cell Transplantation Outcomes

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A B S T R A C T

The association between pre–hematopoietic stem cell transplantation (HSCT) vancomycin-resistant *Enterococcus* (VRE) colonization, HSCT-associated VRE bacteremia, and HSCT mortality is disputed. We studied 161 consecutive patients with acute leukemia who underwent HSCT at our hospital between 2006 and 2014, of whom 109 also received leukemia induction/consolidation on our unit. All inpatients had weekly VRE stool surveillance. Pre-HSCT colonization was not associated with increases in HSCT mortality but did identify a subgroup of HSCT recipients with a higher risk for VRE bacteremia and possibly bacteremia from other organisms. The major risk factor for pre-HSCT colonization was the number of hospital inpatient days between initial admission for leukemia and HSCT. One-third of evaluable patients colonized before HSCT were VRE-culture negative on admission for HSCT; these patients had an increased risk for subsequent VRE stool surveillance positivity but not VRE bacteremia. Molecular typing of VRE isolates obtained before and after HSCT showed that VRE strains frequently change. Postengraftment VRE bacteremia was associated with a much higher mortality than pre-engraftment VRE bacteremia. Pre-engraftment bacteremia from any organism was associated with an alternative donor and resulted in an increase in hospital length of stay and cost. Mortality was similar for pre-engraftment VRE bacteremia and pre-engraftment bacteremia due to other organisms, but mortality associated with post-engraftment VRE bacteremia was higher and largely explained by associated severe graft-versus-host disease and relapsed leukemia. These data emphasize the importance of distinguishing between VRE colonization before HSCT and at HSCT, between pre-engraftment and postengraftment VRE bacteremia, and between VRE bacteremia and bacteremia from other organisms.

INTRODUCTION

Vancomycin-resistant *Enterococcus faecium* (VRE) gastrointestinal colonization and bacteremia are clinically significant complications in patients undergoing hematopoietic stem cell transplantation (HSCT). However, available epidemiological evidence remains conflicted regarding the precise relationships between pre-HSCT VRE colonization, HSCT-associated VRE bacteremia, and mortality. Prior studies reveal differing results as to whether pre-HSCT VRE colonization is a risk factor for HSCT-associated VRE bacteremia [1-3], whether pre-HSCT VRE colonization predicts increased HSCT mortality [3,4], and whether HSCT-associated VRE bacteremia itself causes an increase in HSCT death rates [4-7].

In this study, we re-examine these issues and expand on previous work by distinguishing between colonization before HSCT and colonization at HSCT, between pre-engraftment and postengraftment HSCT-associated VRE bacteremia, and between HSCT-associated VRE bacteremia, bacteremia due to other organisms, and no bacteremia. In addition, we employ molecular strain typing to compare relatedness of VRE strains. Finally, we explore the impact of VRE colonization and infection on the consumption of health care resources.

MATERIALS AND METHODS

Patients

We studied 161 consecutive patients with acute myelogenous leukemia, acute lymphoblastic leukemia, or biphenotypic leukemia who underwent HSCT at the Intermountain acute leukemia and blood and marrow transplant program between 2006 and 2014. One hundred nine of these patients

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had also undergone induction/consolidation therapy on our unit. Patients were housed in individual high-efficiency particulate air–filtered positive-pressure rooms and routinely had central venous catheters inserted. The hematopoietic cell transplantation–specific comorbidity index for each patient was calculated as described [8]. Per our institutional standard of care, all patients undergoing inpatient leukemia induction/consolidation or HSCT were asked to provide a stool sample for VRE culture each Monday. Isolates from all VRE bacteremias and many stools were cryopreserved. VRE-colonized patients were placed into contact isolation (gloves and gowns). Afebrile neutropenic patients undergoing leukemia therapy or HSCT received antimicrobial prophylaxis (levofloxacin, penicillin, and either an echinocandin or antimold triazole). Oral nonabsorbable antimicrobial agents were not used. The usual empiric antibiotic regimen for febrile neutropenia was a carbapenem. Extended gram-positive coverage, usually vancomycin, was added if felt clinically indicated. Total patient costs (direct and indirect), adjusted to 2016 dollars, were estimated by relating total hospital costs to charge codes. Costs, inpatient and outpatient, were calculated from the first day of the preparative regimen to death or a predetermined time period (3 months or 1 year), whichever came first. Patients dying before the time period had their total costs included. The study was approved by the Intermountain Healthcare institutional review board.

Definitions

Patients colonized before HSCT were so identified if they had at least 1 positive VRE stool culture during a hospitalization before initiation of the preparative regimen. Patients were classified as colonized or not at HSCT admission on the basis of a first screening stool culture obtained within 1 week (median, 2 days) of the initiation of the preparative regimen. *Bacteremia* was defined as any positive blood culture in the presence of signs of infection, usually fever. The transplantation day of *neutrophil engraftment* was the first day the absolute neutrophil count exceeded 500 cells/mm^3 for 3 consecutive days. A *pre-engraftment bacteremia* occurred between the first day of the preparative regimen and the day before neutrophil engraftment. A *postengraftment bacteremia* occurred on the day of neutrophil engraftment or afterwards.

VRE Screening and Molecular Analysis

Stools submitted for VRE screening cultures were plated onto bile esculin agar plates and BB L Campylobacter agar plates (Becton Dickinson, Sparks, MD). Vancomycin resistance was confirmed using MicroScan(Beckman Coulter, Brea, CA). Blood cultures were processed using the Phoenix (BD, Franklin Lakes, NJ) automated system. VRE isolates were cryopreserved at –80°C in skim milk broth. Cryopreserved isolates were cultured on 5% sheep's blood trypticase soy agar II agar plates and DNA was extracted with the UltraClean Microbial DNA Isolation Kit (Mo Bio Laboratories, Carlsbad, CA). Molecular typing of isolates was performed with repetitive element PCR utilizing the semi-automated DiversiLab System (bioMerieux, Craponne, France). We defined isolates having a similarity of >97% and no band differences on visual inspection of the electropherogram as *indistinguishable* [9].

Statistical Analysis

Probabilities of colonization, infection, and overall survival were estimated using the Kaplan-Meier method. Univariate analyses of these curves were performed using log-rank tests. Characteristics of different groups were compared using 2-tailed Fisher's exact or Mann-Whitney U tests. After correction within groups for multiple comparisons [10], a P value < .05 was considered significant.

RESULTS

Our cohort of 161 consecutive patients underwent HSCT a median of 3.6 (range, 0 to 140) months after admission for treatment of acute leukemia. The median follow-up from HSCT for all patients was 16 (range, .6 to 120) months and for surviving patients 30 (range, 7.6 to 120) months. One hundred seventeen patients had acute myelogenous leukemia, 38 had acute lymphoblastic leukemia, and 6 had acute biphenotypic leukemia. One hundred thirty-four patients had myeloablative and 27 had nonmyeloablative conditioning. The median age of our cohort was 49 years (range, 18 to 75), almost a decade younger than expected for the leukemic diagnoses reflecting selection for HSCT. An excess of male gender (57%) was expected given the male predominance in adult acute leukemia. The median time from transplantation to neutrophil engraftment was 16 (range, 0 to 55) days. VRE bacteremia developed in 19 (12%) of the 161 patients. Pre-engraftment VRE bacteremia occurred in 10 patients and post-engraftment VRE bacteremia in 9 patients.

The Clinical Significance of VRE Colonization before HSCT

A subgroup of 109 patients who underwent both leukemic induction/consolidation and HSCT at our center were evaluable for VRE colonization before HSCT. Sixty-six patients (61%) had at least 1 stool culture positive for VRE recorded before HSCT. Characteristics and outcomes for patients with and without detected colonization before HSCT are compared in Table 1. Although both groups had similar median intervals between leukemia diagnosis and HSCT, colonized patients had a greater number of hospital inpatient days during this interval.

Patients colonized before HSCT were more likely to have VRE colonization at HSCT admission (Table 1) and to be colonized during HSCT (hazard ratio [HR], 3.8; 95% confidence interval [CI], 2.7 to 6.7). The excess risk of colonization for patients colonized before HSCT occurred during the first 2 weeks after initiation of the preparative regimen, after which the rates of VRE acquisition slowed and the 2 groups were similar (Figure 1A). To determine whether patients had the same VRE molecular strain types during their hospitalization for leukemic induction and at admission for HSCT, we compared the isolates from 22 patients. Only 10 of these (45%) had the same indistinguishable VRE subtype, implying persistent carriage of the same strain. The median intervals between leukemic induction and HSCT were similar between those persistently colonized with the same strain and those with a different strain (3.1 versus 3.0 months, respectively).

Table 1
Comparison of the 109 Patients with or without VRE Colonization before HSCT

Characteristic	VRE+	VRE–	P*
No. of patients	66	43	
Age at leukemia diagnosis, median (range)	49 (18-73)	48 (18-69)	
Gender: female	33 (50%)	12 (28%)	.06
Induction to HSCT, median (range), mo.	3.5 (1.3-54)	3.1 (1.4-28)	
Hospital days before HSCT, median (range),	58 (14-181)	39 (14-97)	.003
VRE stool status at HSCT admission			
Evaluable patients	56 (85%)	34 (79%)	
VRE-negative on admit	19 (34%)	31 (91%)	<.001
Subsequently VRE+	11 (58%)	7 (29%)	.025
Patients with VRE infections after HSCT	23 (32%)	2 (7%)	.001
Pre-engraftment VRE bacteremia	6 (9%)	0	
Postengraftment VRE bacteremia	6 (9%)	0	
VRE UTI	7 (11%)	2 (5%)	
VRE soft-tissue infection	4 (6%)	0	
HSCT cost analysis			
Myeloablative HSCT LOS, median (range), d	36 (24-135)	34 (24-77)	
Costs first 3 months, median (range), $\times 10^5$, $	2.2 (.19-7.5)	1.8 (.16-7.5)	.10
Costs first year, median (range), $\times 10^5$, $	3.4 (.35-9.80)	2.7 (.57-10)	.10

Data presented are n (%) unless otherwise indicated.
UTI indicates urinary tract infection.
* Corrected P values ≤ .1 are indicated.