BRIEF ARTICLE

Risk Factors for Late *Staphylococcus Aureus* Bacteremia after Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Institution, Nested Case-Controlled Study

Coralia N. Mihu,[1] Jenifer Schaub,[1] Sandra Kesh,[1] Ann Jakubowski,[2] Kent Sepkowitz,[1] Eric G. Pamer,[1] Genovefa A. Papanicolaou[1]

We report on the incidence, risk factors, and outcome of late *Staphylococcus aureus* bacteremia (SAB) in a cohort of 709 adult and pediatric patients at Memorial Sloan-Kettering Cancer Center between September 1999 and December 2006. The SAB cases were identified by prospective surveillance and examination of a computerized database. Late SAB was defined as SAB occurring > 50 days post-hematopoietic stem cell transplantation (HSCT). A nested case-controlled study was conducted to identify predictors of late SAB. The incidence of late SAB was 6/100,000 patient-days. The median time from stem cell infusion to incident blood culture was 137 days (range, 55 to 581 days). Eighty-four percent of the cases were community acquired; 40% involved a focal infection. Bacteremia was persistent (>3 days) despite removal of endovascular access in > 50% of cases. Risk factors for late SAB were acute graft-versus-host disease (aGVHD) flare, acute or chronic skin GVHD (cGVHD), corticosteroid use, liver dysfunction, and prolonged hospital length of stay (LOS) post-HSCT. In multivariate models, skin GVHD ($P = .002$) and LOS ($P = .02$) remained significant. The median survival post-SAB was 135 days (range, 1 to 1765 days). Late SAB occurred mainly in the setting of GVHD or corticosteroid therapy. Clinical manifestations were highly variable. Multiple comorbidities, indicated by organ dysfunction and hospitalization, likely contributed to persistence and increased morbidity and mortality. We recommend a high index of suspicion and empiric antistaphylococcal treatment pending culture results in high-risk patients undergoing HSCT.

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KEY WORDS: Late *Staphylococcus aureus* bacteremia, Case-controlled, Allogeneic hematopoietic stem cell transplantation, Mortality, Risk factors

INTRODUCTION

Bacteremia is the most common infection after allogeneic hematopoietic stem cell transplantation (HSCT), with a reported incidence of up to 40% [1]. *Staphylococcus aureus* bacteremia (SAB) has been associated with considerable morbidity and mortality in various clinical settings [2,3]. Despite a predominance of gram-positive organisms, *S aureus* is a rather rare cause of bacteremia in HSCT, with a reported incidence of 1% to 3% [4]. Importantly, the reported mortality attributed to *S aureus* is quite low compared with rates in non-HSCT patients [5]. The present study was conducted to investigate the incidence, risk factors, and outcome of postengraftment SAB.

METHODS

Study Patients

The study was approved by the Memorial Sloan Kettering Cancer Center (MSKCC) Institutional Review Board. The cohort comprised 709 consecutive adult and pediatric patients who underwent allogeneic HSCT at MSKCC between September 1, 1999 and December 31, 2006. Patients were censored at relapse or second HSCT. Cases of late SAB were identified by examining a computerized microbiology database and

From the Department of Medicine, [1]Infectious Disease; and [2]Bone Marrow Transplantation Services, Memorial Sloan Kettering Cancer Center, New York, New York

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Correspondence and reprint requests: G. A. Papanicolaou, Department of Medicine, Infectious Diseases Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 9, New York, NY 10021 (e-mail: papanicg@mskcc.org).

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prospectively collected epidemiology records. Clinical data were extracted from medical records.

Definitions

Late SAB was defined as at least 1 set of blood cultures positive for *S aureus* with clinical signs of infection occurring > 50 days after HSCT. All cultures were processed by the MSKCC Clinical Microbiology Laboratory. Follow-up blood cultures were obtained routinely in patients with positive cultures. SAB was considered nosocomial if the incident blood culture was drawn > 72 hours after admission. SAB was considered sustained if blood cultures were positive for ≥ 3 days within 1 week of the incident blood culture. The recurrence interval was 7 days. Septic shock was defined as a systolic blood pressure < 90 mm Hg, with evidence of peripheral hypoperfusion. Pneumonia was defined as new infiltrates detected on chest radiograph and a positive bronchoalveolar lavage or endotracheal aspirate culture for *S aureus*. Endocarditis was defined by Duke's criteria [6]. A central venous catheter (CVC) was considered the source of infection if bacteremia resolved promptly after catheter removal and if no other focus of infection was identified. Pocket and tunnel infections associated with intravascular devices were defined according to standard criteria [7]. Case fatality was defined as death occurring within 7 days of the incident blood culture.

Time to myeloid engraftment was calculated as the number of days from stem cell infusion to an absolute neutrophil count (ANC) ≥ 1000/mm^3 on 2 consecutive days after stem cell infusion. Secondary neutropenia was defined as ANC ≤ 1000/mm^3 on ≥ 2 consecutive measurements after having achieved neutrophil recovery and within 30 days of SAB. Liver or kidney dysfunction was defined as a ≥ 2 consecutive measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin > 3 times the upper limit of normal and creatinine > 2 times the upper limit of normal, respectively, between day +40 post-HSCT and the date of the incident blood culture. Values for $CD4^+$ and $CD8^+$ lymphocyte subsets and serum IgG levels at 6 months post-HSCT were recorded. Graft-versus-host-disease (GVHD) was graded by standard criteria [8]. Corticosteroid use was defined as ≥ 1 mg/kg/day of methylprednisolone or equivalent for ≥ 14 days within 30 days before the incident blood culture. Use of steroid-sparing immunosuppressants was recorded if administered for ≥ 7 days within 30 days of the incident blood culture. Any antibiotic use for ≥ 7 consecutive days within 30 days of the incident blood culture was recorded. Overall hospital length of stay (LOS) was calculated as the total number of days in the hospital between day 40 post-HSCT and the date of the incident blood culture.

Conditioning regimens containing fractionated total body irradiation (TBI) included thiotepa and cyclophosphamide (Cy) or thiotepa and fludarabine (Flu). The non-TBI–containing regimens included busulfan (Bu) and Cy or Bu and melphalan (Mel). Recipients of unmodified HSCT received standard GVHD prophylaxis with methotrexate (MTX) or (CsA) cyclosporine-A. Recipients of T cell–depleted transplants did not receive any additional GVHD prophylaxis.

Standard care of HSCT recipients included fluconazole and acyclovir starting at cytoreduction. Patients also received *Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole or pentamidine (in case of sulfa allergy) from day −7 to day −3. No routine antibacterial prophylaxis was given to the patients undergoing HSCT until December 2005. Starting on December 1, 2005, adult patients who underwent myeloablative conditioning received vancomycin prophylaxis starting at day -2 relative to stem cell infusion through day +7 post-HSCT.

Statistical Analysis

To determine risk factors for late SAB, we conducted a nested case-controlled study. Three controls for each case were then randomly selected from the same cohort and matched to cases on duration of follow-up, age (within 5 years), sex, and donor relationship. Each variable was initially analyzed in univariate models using conditional logistic regression. Significant variables were then combined into a single multivariate model. The final multivariate model was selected through best-subsets selection, using the score statistic as the selection criterion. Results were considered statistically significant if the P values from the likelihood ratio test were < .05. Survival plots were constructed using Kaplan-Meier method. Differences in survival curves were determined using log-rank test. All data analyses were done using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Incidence of Postengraftment SAB

Table 1 summarizes the characteristics of the cohort of 709 consecutive adult and pediatric patients who underwent HSCT. Median follow-up was 680 days (range, 66 to 2443 days). Twenty-nine of the 709 patients (4.1%) developed SAB. Twenty-six patients (3.6%) developed late SAB, a median of 137 days (range, 52 to 581 days) after HSCT. The incidence of late SAB was 6.0/100,000 patient days; 22 (84.6%) of these cases were community-acquired. The incidence of SAB was similar in adult and pediatric HSCT recipients (3.5% vs 3.8%; P = not significant).