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Empiric use of linezolid in febrile hematology and hematopoietic stem cell transplantation patients colonized with vancomycin-resistant *Enterococcus spp*

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SUMMARY

Objectives: We conducted a retrospective study on the impact of the empiric use of linezolid on mortality in vancomycin-resistant *Enterococcus spp* (VRE)-colonized hematology and hematopoietic stem cell transplantation (HSCT) patients.

Methods: VRE-colonized inpatients for whom complete data were available ($n = 100$) were divided into two groups: those who received empiric linezolid in the course of fever refractory to broad-spectrum antibiotics, replacing the glycopeptide utilized for the previous 48 h, and those who did not (control group). All patients were followed until hospital discharge or death. The impact of linezolid and risk factors for all-cause mortality were evaluated; variables with $p < 0.10$ were analyzed in a multivariate model. A Kaplan–Meier survival analysis was done to compare survival among febrile patients colonized by VRE who received empiric linezolid with patients who did not receive linezolid.

Results: Patients empirically prescribed linezolid were generally younger (median age 33 vs. 44 years; $p = 0.008$) and more likely to be recipients of an allogeneic HSCT (24 (68.6%) vs. 24 (36.9%); $p = 0.009$) than patients who did not receive the drug. Fourteen (21.5%) VRE bloodstream infections were diagnosed, all in patients who did not receive empiric linezolid ($p = 0.002$). In-hospital mortality was comparable in empiric linezolid and non-linezolid users (19 (54.3%) vs. 27 (41.5%), respectively; $p = 0.293$). The Kaplan–Meier survival analysis showed no significant difference in survival comparing the group that received linezolid to the group that did not ($p = 0.72$). Graft-versus-host disease (GVHD; odds ratio (OR) 5.90, 95% confidence interval (CI) 1.46–23.79; $p = 0.012$) and persistence of neutropenia (OR 6.93, 95% CI 1.72–27.94; $p = 0.0065$) were independent predictors of all-cause in-hospital death in HSCT patients, and persistence of neutropenia in non-HSCT patients (OR 8.12, 95% CI 1.22–53.8; $p = 0.030$).

Conclusions: The empiric use of linezolid in VRE-colonized hematology patients had no impact on mortality, which appeared rather to be associated with the persistence of neutropenia in general and GVHD in the HSCT group.

1. Introduction

Vancomycin-resistant *Enterococcus spp* (VRE) infections in hematology and hematopoietic stem cell transplant (HSCT) patients have been gaining attention given the overall increasing

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prevalence of VRE colonization and infection in some countries,[1–3] and the high morbidity and mortality in this patient population.[4] Colonization of the gastrointestinal tract with VRE is postulated to precede VRE infection.[5–9] Bloodstream infection (BSI) due to VRE, in particular, has been linked to increased mortality in this population.[10–14] VRE-attributable mortality, however, is difficult to ascertain due to the severity of illness of the underlying disease in these patients.[15–17]

Anti-VRE antibiotic drugs have reportedly been advocated as empirical agents for the treatment of febrile neutropenia among VRE-colonized patients,[6,18,19] even though data supporting their empirical use in this setting are largely lacking. Resistance to linezolid among VRE, on the other hand, has been reported,[20–22] and is directly associated with its consumption,[22] thus warranting the investigation of this approach to ensure an adequate rationale for the empiric use of linezolid in VRE-colonized patients.

A retrospective study of the impact of empiric use of linezolid and risk factors for all-cause mortality in hematology and HSCT patients colonized by VRE was performed.

2. Methods

2.1. Design

This retrospective study was performed to assess the outcomes of the empiric use of linezolid (Pfizer, NY, USA), prescribed in accordance with the literature recommendations (adult patients, 600 mg intravenous (IV) every 12 h; pediatric patients, 10 mg/kg IV every 8 h), in the course of persistent febrile episodes in hematology and HSCT adult and pediatric patients admitted to the Hematology and Bone Marrow Transplant wards of the Hospital das Clínicas da Universidade de São Paulo (Sao Paulo, Brazil). VRE-colonized patients admitted between January 2005 and May 2007 were considered eligible. Complete paper charts and electronic records holding microbiological data were necessary for inclusion in the study; these were available for 100 patients. A case series describing baseline characteristics and outcomes of VRE-colonized patients receiving linezolid empirically and patients who did not receive this antibiotic (considered the control group) was recorded; risk factors associated with in-hospital mortality were evaluated. The study was approved by the institutional research ethics board (CAPPesq – Ethics Commission for the Analyses of Research Projects, Hospital das Clínicas da Universidade de São Paulo).

2.2. Setting

The study was conducted in a 900-bed tertiary-care teaching hospital in Sao Paulo, Brazil, encompassing a joint unit with eight bone marrow transplant and 15 hematology beds. Local protocols for the treatment of febrile neutropenia in place at the time were largely based on the 1997 guidelines of the Infectious Diseases Society of America (IDSA)[23] and did not advocate the routine use of anti-VRE drugs in VRE-colonized patients. Infectious diseases specialists restrict access to linezolid through an individual case assessment as part of the institutional antimicrobial stewardship program. During the study period, the empiric use of linezolid was considered on a case-basis for VRE-colonized patients upon persistence of fever after 48 h of use of broad Gram-negative bacilli antibiotic coverage and a glycopeptide antibiotic. Whenever linezolid was prescribed, glycopeptide antibiotics were immediately discontinued. Antibiotic therapy was de-escalated and optimized according to microbiological data and was continued for the standard recommended duration according to the site of infection, or for that recommended in the absence of confirmed infection. Discontinuation of antimicrobial therapy, in the absence of isolation of a causative agent, was contingent on completing a minimum of 5 days of treatment and on resolution of fever and recovery of neutrophil counts for 72 h (absolute neutrophil counts (ANC) $>0.5 \times 10^9$ cells/l). Specimens for microbiological diagnosis were collected routinely prior to administration or upon changes in antimicrobial therapy.

2.3. Data collection

Microbiological data and infection control and medical records were reviewed by three investigators (BGM, LFL, SFC). Infections were defined according to the Centers for Disease Control and Prevention nosocomial infection criteria.[24] The following variables were compared between the case and control groups: age, length of hospital stay, underlying hematological disease, type of HSCT, the presence of mucositis or graft-versus-host disease (GVHD) as diagnosed by the assisting hematologist and recorded on the patient's chart, Multinational Association of Supportive Care in Cancer (MASCC) risk index score,[26] use of a central venous catheter (CVC), site of infection, laboratory tests including ANC and platelet counts, duration and severity of neutropenia, and linezolid prescription information. The patients were followed from hospital admission until the first of the following events: in-hospital death or discharge from the hospital.

2.4. VRE surveillance

VRE rectal/peri-anal screening swabs were taken routinely upon admission and were repeated weekly, until colonization was documented or until hospital discharge. Surveillance cultures were seeded directly in VRE-selective medium containing 6 μg/ml of vancomycin. Identification and susceptibility testing, including ampicillin and linezolid susceptibility testing, were performed for all specimens using automated (Vitek; bioMérieux, Hazelwood, MO, USA) and/or disk diffusion methods, the latter following the methodology established by the Clinical and Laboratory Standards Institute (CLSI).

2.5. Statistical analysis

Data analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). The two-tailed Fisher's exact test was used for categorical variables and the Mann–Whitney *U*-test was used for continuous variables. Logistic regression models were developed to identify factors independently associated with in-hospital mortality. All non-overlapping variables with $p < 0.1$ on univariate analysis and that fitted a biological rationale were entered into the model in a single step. The logistic regression model obtained was also applied for subgroup analysis (non-HSCT vs. HSCT). A *p*-value <0.05 was considered to be statistically significant. A Kaplan–Meier survival analysis was done to compare survival among febrile hematology and HSCT patients colonized by VRE who received empiric linezolid with patients who did not receive linezolid.

3. Results

3.1. Setting

A total of 1535 patients were admitted to the hematology and bone marrow transplant wards during the study period. VRE are endemic to these medical units; the period studied was delimited to exclude VRE outbreaks, and no linezolid-resistant strains were observed during the study period. The median length of hospitalization prior to VRE colonization was 10 days (range 0–61 days).