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Health-care associated bacteremia in geriatric cancer patients with febrile neutropenia

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ABSTRACT

Objective: The aim of this study was to determine the epidemiology, clinical manifestations, and outcome of health-care associated bacteremia in geriatric cancer patients with febrile neutropenia.

Materials and Methods: We retrospectively evaluated cancer patients with febrile neutropenia aged ≥60 years with culture proven health-care associated bacteremia between January 2005 and December 2011. The date of the first positive blood culture was regarded as the date of bacteremia onset. Primary outcome was the infection related mortality, defined as the death within 14 days of bacteremia onset.

Results: The two most common pathogens responsible for bacteremia were *Staphylococcus epidermidis* (36.1%) and *Escherichia coli* (31.5%), with high rates of methicillin resistance and extended-spectrum β-lactamase (ESBL) production, respectively. There were no statistically significant differences in infection related mortality rate according to the type of malignancy ($p=0.776$). By the univariate analysis, factors associated with 14 day mortality among febrile neutropenic episodes were prolonged neutropenia ($p=0.024$), persistent fever ($p=0.001$), hospitalization in ICU ($p<0.001$) and the initial clinical presentations including respiratory failure ($p<0.001$), hepatic failure ($p=0.013$), hematological failure ($p<0.001$), neurological failure ($p<0.001$), severe sepsis ($p<0.001$), and septic shock ($p=0.036$). Multivariate analysis showed that persistent fever was an independent factor associated with infection related mortality (odds ratio, 18.0; 95% confidence interval, 5.2–62.6; $p<0.001$).

Conclusions: The only independent risk factor for mortality was persistent fever. Although the most frequently isolated pathogens were *S. epidermidis* and *E. coli*, high rates of methicillin resistance and ESBL production were found respectively.

1. Introduction

Despite treatment with potent and broad spectrum antibiotics, bacterial infections remain a severe problem in cancer patients, with or without neutropenia. Bacteremia is an important cause of the most severe infection, resulting in high mortality and morbidity rates in cancer patients with febrile neutropenia. Bacteremia may be related to the highly immunosuppressant medications and the aggressive diagnostic and/or therapeutic tools used to manage different types of cancer. The proportions of Gram-positive and Gram-negative pathogens causing bacteremia in patients with febrile neutropenia have been found to differ by patient age and country.[1,2] Although extended-spectrum β-lactamase (ESBL)-producing pathogens have been associated

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with poor prognosis in cancer patients with neutropenia, a recent study did not find an association between neutropenia and increased mortality in cancer patients with ESBL-producing bacteremia.[3] Health-care associated bacteremia is a trend definition between community and hospital acquired. Because of shorter hospital stays, increased outpatient delivery of care, and increased numbers of immunosuppressed patients, some changes in previous definitions of community- and hospital-acquired bacteremia were required.[4] Despite increasing concerns about antimicrobial resistance and emerging pathogens among blood culture isolates, and the recommendations about the coverage of resistant pathogens in empirical treatment of cancer patients with febrile neutropenia, little is known about the epidemiology and the outcome of bacteremia in elderly neutropenic cancer patients with health-care associated bacteremia.[3–5] We have therefore investigated the epidemiology, clinical manifestations, and outcome of health-care associated bacteremia in geriatric cancer patients with febrile neutropenia.

2. Materials and Methods

2.1. Hospital Setting and Study Design

Bulent Ecevit University Teaching and Research Hospital is a 450-bed tertiary care hospital in Zonguldak, Turkey. The hospital contains all major wards, including those associated with medical and surgical subspecialties, and medical and surgical intensive care units (ICUs). This retrospective study included cancer patients with febrile neutropenia, aged ≥60 years, hospitalized between January 2005 and December 2011 with bloodstream infections. The study protocol was approved by the Ethics Committee of Bulent Ecevit University Teaching and Research Hospital.

2.2. Data Collection

All cancer patients with febrile neutropenia, aged ≥60 years, and hospitalized with culture proven bloodstream infections between January 2005 and December 2011 were included. Their clinical characteristics, comorbidities, initial manifestations, antimicrobial therapy, clinical outcome, host factors causing immunosuppression, and Multinational Association for Supportive Care in Cancer (MASCC) risk index score were recorded. The date of the first positive blood culture was regarded as the date of bacteremia onset. Because coagulase-negative staphylococci are frequently encountered contaminants, at least two positive blood cultures, drawn on separate occasions within a 48-hour period, were required for patients to be classified as having coagulase-negative staphylococcal bacteremia.

2.3. Definitions

Types of cancer that affected the blood, bone marrow, and lymph nodes were categorized as hematological malignancies, whereas malignant tumors involving any tissue or organ were classified as solid tumors. Recent immunosuppressive therapy was defined as treatment with ≥10 mg/day prednisone or equivalent for more than two weeks, and chemotherapy within four weeks before bacteremia onset.[3]

Antibiotic therapy was considered "appropriate" if the drugs exhibited in vitro activity against the isolated microorganisms. Antimicrobial treatment was defined as "inappropriate" when the prescribed agents were not effective in vitro against the isolated microorganisms. Neutropenia was defined as a neutrophil count of <500 cells/mm^3 or a count of <1000 cells/mm^3 with a predicted decrease of <500 cells/mm^3 within the next 48–72 h. Fever was defined as a single oral temperature of 38.3 °C or an oral temperature of 38 °C lasting for more than 1 h.[6] Health-care associated bacteremia was defined as a positive blood culture obtained from a patient at the time of hospital admission or within 48 h of admission if the patient fulfilled any of the criteria: 1) patients who had received intravenous therapy at home; had received wound care or specialized nursing care through a health-care agency, family, or friends; or had self-administered intravenous medical therapy 30 days before bacteremia; 2) patients who had attended a hospital or hemodialysis clinic or had received intravenous chemotherapy 30 days before bacteremia; 3) patients who were hospitalized in an acute care hospital within 30 days before the bacteremia; and 4) patients who had resided in a nursing home.[5] Hypotension was defined as a systolic blood pressure<90 mm Hg or a need for inotropic support to maintain blood pressure. Respiratory failure was defined as an arterial oxygen pressure<60 mm Hg while breathing room air or a need for mechanical ventilation.[6] Other organ failures were defined according to organ dysfunctions and categorized as renal, hepatic, neurologic, cardiovascular or hematological failure.[7] Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension that could be reversed by adequate fluid resuscitation.[8] After the onset of febrile neutropenia, a fever of >38 °C persisting during hospitalization or until death despite antibacterial therapy effective against the isolated microorganism from the blood culture was defined as persistent fever. Prolonged neutropenia was defined as neutropenia lasting >10 days after a diagnosis of febrile neutropenia or until death. MASCC risk index score was determined as described, with a risk score of <21 indicating that a patient was at high risk for complications and death.[9] Sources of bloodstream infections were categorized as primary and secondary bloodstream infections. Primary bloodstream infections including intravascular device-associated infections were defined according to the National Nosocomial Infections Surveillance System.[10,11] Secondary bloodstream infections were declared to be present when an organism isolated from a blood culture was related to an infection at another site.[10] Infection related mortality was defined as the rate of death within 14 days after bacteremia onset.[3]

2.4. Isolation and Identification of the Microorganisms from Cultures

Blood cultures were performed in the BACTEC 9120 blood culture system (Becton Dickinson, USA). Isolates were identified using conventional methods, and when required, the results were confirmed by semi-automated API systems (bioMérieux, Marcyl'Etoile, France). Antibiotic susceptibility tests were performed by the Kirby–Bauer disk diffusion method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[12]