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ORIGINAL ARTICLE

Risk factors for sepsis-related death in children and adolescents with hematologic and malignant diseases

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risk factor;
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vancomycin

Background: The aim of this study was to elucidate risk factors for mortality after developing sepsis in pediatric patients with hematologic and malignant disorders.
Methods: A total of 90 patients (43 boys, 47 girls) with various hematologic and malignant diseases who experienced sepsis between June 2006 and March 2014 were enrolled. Clinical and laboratory features of 134 episodes of sepsis observed in the 90 patients were compared between those with and without sepsis-related death which was defined as death within 14 days after sepsis.
Results: Age at hospitalization, sex, and type of underlying disease did not differ between patients with and without sepsis-related death. Sepsis episode-based univariate analysis identified patients with a history of relapse or in a refractory state of underlying disease ($p < 0.01$), those with high C-reactive protein concentrations ($\geq$50 mg/L) at the beginning of fever ($p < 0.01$), those who had undergone hematopoietic stem cell transplantation ($p < 0.01$), and those who were forced to change initial antibiotics ($p = 0.02$) because of being at high risk of sepsis-related death. The former two factors were further confirmed by multivariate analysis. More than half (52.9%) the isolates from sepsis-related death were Gram-positive cocci resistant to β-lactam antibiotics, but susceptible to vancomycin.
Conclusion: It was found that a history of relapse, a refractory state of underlying disease, and high C-reactive protein concentrations at the beginning of fever were significant risk factors

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for mortality after developing sepsis. Survival rate of patients with risk factors raised in this study might be improved by early introduction of vancomycin.

Introduction

Recent advances in chemotherapy and hematopoietic stem cell transplantation (HSCT) have improved the survival rate of pediatric patients with hematologic and malignant disorders and bone marrow failure syndrome. Nonetheless, the accompanying intensification of therapy, such as multidrug chemotherapy and HSCT, has led to an increased incidence of severe infection including sepsis. Sepsis is still a major cause of morbidity and mortality in patients with hematologic and malignant diseases, although various antibacterial/antifungal treatments have been developed. Limited data characterizing mortality after developing sepsis have been reported for children and adolescents.[1–4] New medical treatment strategies might be produced by the identification of risk profiles, and may lead to better survival. Thus, the aim of this study was to elucidate the risk factors for mortality after developing sepsis in children and adolescents with hematologic and malignant disorders receiving chemotherapy, immunosuppressive therapy, and HSCT.

Methods

Patients

A total of 90 consecutive patients (43 boys, 47 girls) at Sapporo Hokuyu Hospital, Sapporo, Japan with various hematologic malignancies, aplastic anemia, or solid tumors who experienced sepsis following chemotherapy, immunosuppressive therapy, and HSCT between June 2006 and March 2014 were enrolled in this study. The age at admission ranged from 4 months to 24 years (median, 8 years). Forty-three patients had acute lymphoblastic leukemia, 25 had acute myeloid leukemia, four had neuroblastoma, three had aplastic anemia, three had myelodysplastic syndrome (including juvenile myelomonocytic leukemia), two had non-Hodgkin lymphoma, two had hepatoblastoma, two had rhabdomyosarcoma, one had congenital dyserythropoietic anemia, and five had other malignant diseases including retinoblastoma, alveolar soft part sarcoma, dermatofibrosarcoma protuberans, epithelioid sarcoma, and pancreatic neuroendocrine tumor. During the study period, 22 patients received HSCT: 21 of them received allogeneic HSCT and one received autologous HSCT. A total of 134 episodes of sepsis were observed in the 90 patients during the study period.

Informed consent was obtained from the patients and/or their parents, according to guidelines based on the tenets of the revised Helsinki protocol. The institutional review board of Sapporo Hokuyu Hospital approved this project.

Definitions of sepsis, fever, neutropenia, and sepsis-related death

Sepsis is defined as systemic inflammatory response syndrome in the presence of suspected or proven infection and organ dysfunction according to international consensus guideline[5,6]; however, in this study, we dealt with the cases in which bacterial/fungal pathogens were isolated from blood of patients. When bacteria that typically colonize the skin, such as coagulase-negative staphylococci, corynebacteriae other than *Corynebacterium jeikeium*, and other skin contaminants, were isolated, at least two consecutive blood cultures were analyzed to confirm the pathogenicity of the isolates. Blood cultures were performed in response to a sign of infection, which was typically fever. Fever was defined in this study as an axillary temperature of $\geq$37.5°C on two occasions at least 1 hour apart or a single axillary temperature $>$38.0°C. Neutropenia was defined as an absolute neutrophil count of $<0.5 \times 10^9$/L.

When evaluating the prognosis of sepsis, it is difficult to distinguish strictly whether patients died from sepsis or not. The prognosis of sepsis is often evaluated by the death rate at 28 days after sepsis development in such as an intensive care area[7]; however, when an evaluation period becomes longer in patients with hematological and malignant disease, involvement of factors of death other than sepsis (for example, death due to underlying malignant disease) might increase. Therefore, we decided to analyze prognostic factors of sepsis using the concept of *sepsis-related death*, which was defined as death within 14 days after developing sepsis.

Analytic procedures

To evaluate the background of the enrolled patients, sex, age at hospitalization, and type of underlying disease were compared between patients (a total of 90 patients) with and without sepsis-related death.

Meanwhile, to evaluate the risk factors of sepsis-related death, a total of 134 sepsis episodes observed in the 90 patients were analyzed between patients with and without sepsis-related death for factors including laboratory data at the beginning of fever, condition of underlying disease (history of relapse or refractory state), insertion of a central venous catheter, history of HSCT, changes of initial antibiotics due to prolonged or recurrent fever, and type of isolated pathogen. Data were analyzed as of May 1, 2014.

Infection prophylaxis

Trimethoprim–sulfamethoxazole was prescribed to all patients for the prevention of *Pneumocystis jirovecii*