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ORIGINAL ARTICLE

Risk factors and outcomes of cytomegalovirus viremia in pediatric hematopoietic stem cell transplantation patients

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Abstract *Background:* Cytomegalovirus (CMV) is a major pathogen causing significant mortality and morbidity in immunocompromised hosts. It is important to find risk factors associated with CMV viremia and its outcome.
Methods: We investigated the incidence, time of onset, risk factors for CMV viremia, and characteristics of CMV diseases in 57 pediatric patients receiving hematopoietic stem cell transplantation (HSCT). Between August 2011 and March 2014, cases of pediatric HSCT patients at the National Taiwan University Children's Hospital were reviewed. Viremia was identified by plasma CMV real-time polymerase chain reaction (RT-PCR) assay.
Results: Eighteen (32%) of the 57 patients developed CMV viremia at a median of 23 days post-HSCT (range −3 to +721 days). Eighty-nine percent (16/18) of CMV viremia occurred within 100 days posttransplantation. Four patients finally had CMV diseases (1 with CMV colitis and 3 with CMV pneumonitis) and one patient died of CMV pneumonitis complicated with pulmonary hemorrhage and sepsis. Significant risk factors associated with CMV viremia via univariate analysis include older age ($p = 0.03$), leukemic patients [odds ratio (OR): 5.2, 95% confidence interval (CI): 1.52∼17.7, $p = 0.008$), allogeneic HSCT (OR: 14.57, 95% CI: 1.76∼120.5,

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$p = 0.002$), antithymoglobulin (ATG) use before transplantation (OR: 5.09, 95% CI: 1.52∼16.9, $p = 0.007$), graft-versus-host disease (GvHD) (OR: 10.1, 95% CI: 2.7∼38.7, $p < 0.001$), and gastrointestinal GvHD (OR: 10.9, 95% CI: 2.72∼43.9, $p = 0.001$).
Conclusion: In pediatric posttransplantation patients, CMV viremia mostly occurred within 100 days after transplantation. Risk factors associated with CMV viremia include older diagnostic age, leukemic patients, unrelated donor HSCT, pretransplant ATG use, GvHD, and gastrointestinal GvHD.

Introduction

Cytomegalovirus (CMV), is a virus which belongs to the human herpesviruses, betaherpesviruses. It is a major pathogen causing significant mortality in immunocompromised hosts, such as prematurity and posttransplantation patients.[1,2] From previous studies, the incidence of CMV viremia in pediatric post bone marrow transplantation patients was variable, from 12.8% to 41%.[2–5] The clinical manifestations of CMV infection range from asymptomatic infection, that is, active CMV replication in the blood in the absence of clinical symptoms or organ failure, to CMV disease, characterized by CMV infection with systemic end-organ involvement.[5]

Previous known risk factors of CMV reactivation were CMV serostatus, transplantation type, T-cell depletion regimen, and graft-versus-host-disease (GvHD) development.[3,4,6,7] The objective of this retrospective study was to evaluate the incidence and timing of CMV viremia in a pediatric population who had received hematopoietic stem cell transplantation (HSCT). The risk factors for CMV viremia were studied and characteristics of CMV disease are described.

Patients and methods

Study design and data collection

This study was approved by the ethics committee of National Taiwan University Hospital, Taiwan. We retrospectively reviewed 57 pediatric patients receiving HSCT at the National Taiwan University Hospital during August 2011 to March 2014. No intervention or clinical specimen was collected from patients. All of the information of the patients in this study was obtained from medical records. We collected their demographics, underlying diseases, serostatus, HSCT type and post-HSCT condition, antithymoglobulin (ATG) use, medications, and outcomes.

Identifications and definitions

Currently, quantitative polymerase chain reaction (PCR) assays of plasma samples have become the most common way in the determination of viral load during CMV infection of transplant patients. In this study, CMV real-time PCR (RT-PCR) was performed for quantitation of plasma CMV viremia and bronchoalveolar lavage fluid using COBAS AmpliPrep/COBAS TaqMan CMV Test (Roche Molecular Systems, Inc., Branchburg, NJ, USA), the first U.S. Food and Drug Administration (FDA)-approved assay. The quantitated cut-off level of this method was 150 copies/mL. CMV viremia was defined by positive CMV-specific RT-PCR in plasma. Since conditioning chemotherapy of these patients, plasma CMV PCR was checked by weekly surveillance, which would continue until patients were discharged or had a negative plasma CMV PCR result.

Diagnosis of CMV disease was based on positive CMV viremia and either one of the following: the presence of appropriate symptoms (fever, and/or organ associated symptoms, such as cough/diarrhea, etc.) combined with a positive CMV RT-PCR from the coherent specimen (e.g., pneumonia with positive CMV RT-PCR from bronchoalveolar lavage fluid), or a tissue biopsy specimen that was CMV-positive by either culture or immunohistochemical staining.[2,8,9]

Statistical analysis

All analyses were performed using PASW version 18.0 (SPSS, Chicago, IL, USA). Comparisons between the CMV viremia group and nonviremia group were performed using the Mantel-Haenszel chi-square test for categorical variables to calculate odds ratio (OR) and 95% confidence interval (CI) and using the Mann-Whitney *U* test and Wilcoxon signed rank test for continuous variables. Multivariate analysis was performed using multiple logistic regression. A p value < 0.05 was considered to be statistically significant. All results of significance are reported as two-tailed.

Results

Demographics

From August 2011 to March 2014, 60 patients who received HSCT were initially reviewed in the pediatric department of National Taiwan University Hospital. However, three patients were excluded: one patient had disease relapse on posttransplantation Day +27 and finally expired due to Gram-negative bacteria sepsis, and the other two patients experienced severe sepsis immediately after HSCT and expired on posttransplantation Day +9 and Day +28, respectively. Therefore, a total of 57 patients were