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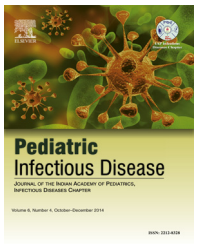

Original Article

Cytomegalovirus infection in children after bone marrow transplantation: Risk factors, clinical aspects and outcomes

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ABSTRACT

Background and objectives: Cytomegalovirus (CMV) infection remains the most common and potentially severe viral complication in patients given hematopoietic stem cell transplantation. The aim of this study was to determine the incidence, risk factors and outcomes of CMV infection in pediatric BMT unit.

Material and methods: This study was a retrospective analysis of clinical, laboratory and outcome data of 131 pediatric patients who underwent BMT.

Results: The mean age of the study population was 6.5 ± 4 years. Out of 131 pediatric patients, 85 were males (64.9%). Majority of patients had hematological disorder/malignancy ($n = 101$; 77%) followed by solid tumors ($n = 30$; 23%). Most of them received allogeneic transplant ($n = 92$; 70.2%). CMV reactivation was observed in 38 (29%) patients; out of them, only ($n = 3$; 2.3%) had clinical manifestation/organ involvement and most cases of CMV were resolved ($n = 35$; 26.7%). Benign hematological disorder, conditioning regimen containing ATG, allogeneic BMT, graft-versus-host disease (GVHD) prophylaxis used and development of GVHD were identifiable risk factors in all patients, and lymphopenia $<300/mm^3$ ($p = 0.047$) was the only identifiable risk factors in allogeneic BMT patients associated with development CMV reactivation. Patients, who had CMV reactivation had significantly higher rate of GVHD (31.6% vs 15.1%; $p = 0.031$), however relapse rate (21% vs 25.8%) and mortality rate (22.5% vs 33.3%) in patients with CMV reactivation vs no CMV reactivation respectively were not statistically significant. Overall survival and event free survival of patients with and without CMV antigenemia were also comparable.

Conclusions: Antigenemia-guided pre-emptive strategy with ganciclovir was very affective and CMV reactivation tended not to affect the outcome in our study cohort.

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1. Introduction

Cytomegalovirus (CMV) infection remains the most common and potentially severe viral complication in patients undergoing hematopoietic stem cell transplantation (HSCT).[1] Seropositivity for CMV is an independent risk factor for mortality, even in recipients of matched sibling or unrelated donor transplants.

The manifestations of CMV range from asymptomatic infection, defined as active CMV replication in the blood in the absence of clinical manifestations or organ failure abnormalities, to CMV disease, characterized by CMV infection with clinical symptoms or organ function abnormalities.[2] Diagnostic procedures to assess the viral load have improved greatly with the increased use of antigenemia, CMV DNA, and immediate early-messenger RNA.[3] Many conditions determine the risk of developing CMV reactivation or disease after bone marrow transplant with serologic status of donor and recipient, type of bone marrow transplant, presence of graft-versus-host disease (GVHD) being the most studied.[4] However, time and quality of immune reconstitution seem to be the pivotal factors. Pneumonia and gastrointestinal involvement are the most frequently documented clinical pictures with late-onset CMV reactivation or disease representing a new challenge.[5]

CMV prophylaxis or pre-emptive therapy adopted during the last few years in allogeneic HSCT recipients has changed the natural history of the disease, reducing the risk of CMV disease, CMV associated death, transplant-related mortality, and has prolonged the period at risk.[6]

Specific studies on children regarding post-BMT CMV infection are lacking, and majority of data are derived from studies performed on adults.[1] Thus, in this single-center, retrospective study, we analyzed the medical records of 131 pediatric patients who underwent BMT to determine the incidence of CMV infection/reactivation and disease and to identify the important risk factors, clinical aspects and outcomes of CMV infection/reactivation in post-BMT pediatric patients at our tertiary health care facility.

2. Material and methods

2.1. Study design and setting

This study was a retrospective analysis of clinical and laboratory data of post-BMT pediatric patients. We included all pediatric patients consecutively underwent bone marrow transplantation in our pediatric BMT unit over a period of 10 years from 2005 to 2014.

Our hospital is a tertiary health care facility and is accredited by the international arm of the Joint Commission International Accreditation Survey (JCIA). There is a 20-bed, pediatric hematology/oncology ward along with a 5-bed BMT unit within the hematology/oncology ward. Total of 131 pediatric patients underwent BMT in the last 10 years duration and average BMT was 13 per year.

2.2. Patient population and definition

Patients from one month to 15 years of age, who were admitted to the pediatric BMT unit for transplantation from 2005 to 2014, were included in this study. Post-BMT patients with CMV reactivation was identified and compared with the rest of post-BMT patients to identify the risk factors, any difference in clinical manifestations and their outcomes. For definition of CMV reactivation and viremia or infection, investigations and management in this study American Society for Blood and Marrow Transplantation (2009) Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients were accepted.[4]

2.3. CMV infection prophylaxis

Pre-emptive therapy (<100 days post-HCT):

- Administer to all HCT recipients (all ages) with evidence of CMV infection in blood by antigenemia, PCR more than 500 copies/ml for CMV DNA or detection of CMV mRNA.
- Ganciclovir, 5 mg/kg/dose, intravenously (i.v.) induction: Twice daily for 7–14 days tell CMV PCR titer is less than 500 copies/ml for two consecutive readings then start maintenance with valganciclovir once daily dose (mg) = 7 × body surface area × creatinine clearance for another 7–14 days.
- *Note*: Continue screening for CMV reactivation weekly and re-treat if screening tests become positive after discontinuation of therapy.

2.4. Data collection

All patients who had diagnosis codes for both neoplastic disease (International Classification of Diseases, 9th revision, clinical modification [ICD-9-CM] code 140-239), nonmalignant disease and bone marrow transplantation, and 15 years or younger was identified by using health information management system and internal BMT registry which records all the MBT patients were included in this analysis. For those patients, who had more than one BMT, each BMT was counted and analyzed as separate case.

The primary outcome of this analysis was to identify the risk factors for CMV reactivation/infection and outcomes (GVHD, survival rate and mortality). Relevant covariates data were collected including demographic features, age, gender, primary diagnosis, phase of chemotherapy (if applicable), clinical features at presentation, duration of symptoms, initial laboratory work up including CMV status and radiological finding (if applicable) and microbiological data, management and outcomes. Underlying disease (acute leukemia, chronic leukemia, solid tumors and nonmalignant diseases), type of donors, transplant type, conditioning regimen, etc. Pre-transplant CMV status of all recipients and donors along with post-BMT assessment, investigations and prophylaxis and management of CMV was also be recorded. All patients were treated as inpatients following the American Society for Blood and Marrow Transplantation (2009) Guidelines for Preventing