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HHV-6 infection after allogeneic hematopoietic stem cell transplantation: From chromosomal integration to viral co-infections and T-cell reconstitution patterns

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Summary *Objectives:* Human herpes virus 6 (HHV-6) can reactivate after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and may be associated with significant clinical manifestations.
Methods: Case control study of HHV-6 infections after allo-HSCT. Chromosomal integration (ciHHV-6) for viral loads $\geq$ 5.5-log10 copies/mL was investigated. Viral co-infections, T-cell

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recovery, risk factors and outcome were compared in HHV-6- and non-HHV-6-infected patients. Antiviral treatment strategies were reviewed.

Results: Among 366 adult allo-HSCT recipients, 75 HHV-6 infections occurred. Three (4%) recipients were ciHHV-6. HHV-6 infections were associated with CMV ($p = 0.05$; sdHR 1.73, CI 0.99−3.02) and/or BKV infections ($p < 0.0001$; sdHR 4.63, CI 2.04−10.53) but not EBV reactivation ($p = 0.34$). A slower CD8+ T-cells recovery was observed until 6 months after allo-HSCT in the HHV-6-infected group ($p < 0.001$), independently of acute and/or chronic graft-*versus*-host disease. The overall probability of survival after allo-HSCT was diminished for active HHV-6-infected patients ($p = 0.0326$). Cord blood unit recipients had a higher risk of developing HHV-6 infection compared to bone marrow recipients ($p = 0.0007$; sdHR 3.82, CI 1.76−8.27). Anti-HHV-6 treatment achieved complete response in only 2/3 of the cases.

Conclusions: In this series of allo-HSCT recipients, 4% were ciHHV-6, active HHV-6 infection was likely associated with CMV and BKV co-reactivations, delayed CD8+ T-cell recovery and poorer outcome.

Introduction

Human herpes viruses 6 (HHV-6) include two separate species HHV-6A and HHV-6B that infect nearly all individuals during early infancy. HHV-6B is the causative agent of exanthema subitum, a childhood disease characterized by high fever and a mild skin rash, occasionally complicated by seizures or encephalitis; HHV-6A has not been etiologically linked to any disease.[1] HHV-6 establish life-long latency with a strong tropism for hematopoietic cells, including CD34+ progenitor stem cells.[2–4] *In vitro* studies have shown that replication can occur in these latter cells through hematopoietic differentiation.[5] HHV-6 reactivation is recognized as a pathogenic infection in immunocompromised hosts, particularly after allogeneic hematopoietic stem cell transplantation (allo-HSCT) throughout the aplasia-related immunodeficiency phase and the immunosuppressive therapy implemented for prevention of graft-*versus*-host disease (GvHD).[6] HHV-6 genome has the ability to integrate into human chromosomes of cells, which can be transmitted as germinal cells to offspring and through allo-HSCT (Mendelian inheritance). This condition is present in ~1% of the population and its implication in HHV-6 central nervous system (CNS) disease is discussed.[7–11]

HHV-6 infection after allo-HSCT is estimated to occur from 20 to 72% of the cases and HHV-6B reactivation is the rule rather than HHV-6A.[8,11–18] In that setting, HHV-6-related clinical manifestations range from febrile rash to the severe post-transplantation acute limbic encephalitis (PALE).[13,18,19] Biologically, HHV-6 infection is frequently associated with liver dysfunction,[20] hematopoietic recovery impairment.[17,21–23] Reported risk factors associated with HHV-6 infection include HLA mismatch, steroid treatment, the use of either unrelated donor or cord blood unit (CBU) grafts.[12,14,15,18] In addition, HHV-6 infection may increase the risk of acute GvHD and facilitate superinfections with cytomegalovirus (CMV).[13,24] PALE is the most serious complication linked to HHV-6 infection, commonly referred as the key criterion accounting for greater morbidity and lethality.[16,25,26]

As several aspects of HHV-6 infection still need to be addressed, this study focuses on 75 cases after allo-HSCT. We have investigated the possibility of chromosomally integrated human HHV-6 in recipients with whole blood HHV-6 levels that exceed 5.5-log10 copies/mL before or after allo-HSCT. We have tested the hypothesis that HHV-6 infections may correlate with other opportunistic and challenging virus infection(s) such as CMV, BK virus (BKV) and EBV as well as a slow CD4+ and CD8+ T cell recovery. We have determined HHV-6 infection incidence, risk factors, and impact of HHV-6 infection on transplantation outcome. Finally, therapeutic strategies applied to HHV-6-infected patients have been examined.

Materials and methods

Patients, donors and disease characteristics

Patient's baseline characteristics are summarized in Table 1. According to the centre practice, whole blood quantitative HHV-6 DNA was measured once every 2 weeks from allo-HSCT to day 90, and monthly thereafter until month 12 post-allo-HSCT. The threshold delimiting HHV-6 infection was a whole blood HHV-6 DNAaemia ≥3-log10 copies/mL. Active HHV-6 infection and/or presence of ciHHV-6 in donor or recipient cells required to collect ≥2 consecutive HHV-6 DNAaemia above 3-log10 copies/mL. HHV-6-associated encephalitis was part of HHV-6 diseases defined as the occurrence of central nervous system (CNS) disorders including PALE associated with a positive PCR for HHV-6 in the cerebrospinal fluid (CSF) of non ciHHV-6 individuals and discussed for ciHHV-6 individuals.[6,12] Simultaneous co-infections with CMV, EBV and BKV were documented. CMV infection was defined as any level of blood CMV DNA above 3-log10 copies/mL.[27] EBV infection was defined as any level of blood EBV DNA above 4-log10 copies/mL.[28] The diagnosis of BKV infection relied on the presence of haemorrhagic cystitis defined by the association of hematuria with urinary symptoms and positive BKV viruria and/or viremia, as previously defined.[29]

Viral monitoring of HHV-6, CMV, EBV and BKV by PCR

Viral DNA was extracted by an automatic nucleic acid platform (NucliSENS® EasyMAG™ BioMérieux) from a whole blood sample, as recommended by manufacturer's