HHV-6 Reactivation and Associated Sequelae after Hematopoietic Cell Transplantation.

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Human herpesvirus 6 (HHV-6) reactivation has been associated with acute graft-versus-host-disease (aGVHD), cytomegalovirus reactivation, and mortality after allogeneic hematopoietic cell transplantation (HCT), but previous studies have yielded inconsistent results. We performed a large prospective study of allogeneic HCT recipients in order to more definitively define the relationships between HHV-6 and these important outcomes. Plasma specimens were collected prospectively from 315 allogeneic HCT recipients and tested for HHV-6 DNA at baseline and twice weekly for 12 weeks. Cox proportional hazards models were used to evaluate the time-dependent associations between HHV-6 reactivation and the targeted outcomes. HHV-6 was detected in 111 of 315 patients (35%) at a median of 20 days after HCT. HHV-6 reactivation was associated with subsequent cytomegalovirus reactivation (adjusted hazard ratio [aHR], 1.9; 95% confidence interval [CI], 1.3-2.8; P = .002). High-level HHV-6 (>1,000 HHV-6DNA copies/mL) was associated with subsequent grades II to IV aGVHD (aHR, 2.4; 95% CI, 1.60-3.6; P < .001). High-level HHV-6 reactivation was also associated with nonrelapse mortality (aHR, 2.7; 95% CI, 1.2-6.3; P = .02). HHV-6 reactivation was independently and quantitatively associated with increased risk of subsequent cytomegalovirus reactivation, aGVHD, and mortality after HCT. A randomized antiviral trial is warranted to establish causality between HHV-6 and these endpoints and to determine if reducing HHV-6 reactivation will improve outcome after HCT.

The complex relationship between human herpesvirus 6 and acute graft-versus-host disease.


The most frequent manifestation of human herpesvirus 6 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation (HSCT) is febrile rash, raising the question of its relationship with graft-versus-host disease (GVHD). In this retrospective analysis of 365 patients who underwent allogeneic HSCT, HHV-6 reactivation was significantly associated with cord blood transplantation (hazard ratio [HR], 3.20; P < .0001) and the use of unrelated donors (HR, 2.02; P = .008). On multivariate analysis, previous GVHD was a predictive factor for HHV-6 reactivation (HR, 1.80; P = .01), and previous HHV-6 reactivation was a predictive factor for acute GVHD (HR, 1.66; P = .03). Nineteen patients with no pathological evidence of GVHD later developed severe clinical GVHD (grade III-IV), suggesting the role of HHV-6 as a trigger for severe GVHD. Furthermore, 17 patients without histopathological GVHD demonstrated a significant lymphoid infiltrate suggesting "pure" HHV-6-related manifestations, and these patients could have been spared steroid therapy.
Correlations of human herpesvirus 6B and CMV infection with acute GVHD in recipients of allogeneic haematopoietic stem cell transplantation.

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Human herpesvirus 6 (HHV-6) and CMV reactivation were monitored in a cohort of 72 consecutive haematopoietic stem cell transplant (HSCT) patients using RQ-PCR and antigenaemia assay, respectively. The association between acute GVHD (aGVHD) and HHV-6B/CMV was evaluated. We found that on day 100 the cumulative incidence of grades I-IV aGVHD, grades II-IV aGVHD and grades III-IV aGVHD was 55.6, 27.8 and 13.9%, respectively. Multivariate analysis indicated that HHV-6B reactivation was closely correlated with a higher probability of grade II-IV aGVHD by day 30 (Hazard ratio (HR), 8.9; 95% confidence interval (CI), 2.6-31.0; P=0.0006), by day 50 (HR, 6.1; 95% CI, 2.1-17.8; P=0.0010) and by day 100 (HR, 4.8; 95% CI, 1.7-13.6; P=0.0028). However, CMV reactivation did not significantly affect the development of aGVHD by day 50 (HR, 0.8; 95% CI, 0.1-6.7; P=0.8236) and by day 100 (HR, 0.5; 95% CI, 0.1-4.4; P=0.5330) after HSCT. In conclusion, this study demonstrated that active HHV-6B infection, but not CMV, is significantly associated with an increased risk of aGVHD development after HSCT.

Human herpes virus 6 plasma DNA positivity after hematopoietic stem cell transplantation in children: an important risk factor for clinical outcome.

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Human herpes virus 6 (HHV6) is known to reactivate after hematopoietic stem cell transplantation (HSCT), and has been suggested to be associated with severe clinical manifestations in adults. The clinical significance in children remains unclear. We investigated the incidence of HHV6 reactivation in relation to HSCT-associated morbidity and mortality in children. Between January 2004 and May 2006, 58 pediatric patients, median age 7.6 years (range: 0.1-18.1 years), received their first allogeneic HSCT. After HSCT, HHV6, Epstein Barr Virus (EBV), cytomegalovirus (CMV), and adenovirus (AdV)-plasma loads were weekly measured by quantitative PCR. Clinical features, engraftment, graft-versus-host disease (GVHD), and HSCT-associated mortality and morbidity were monitored. HHV6 reactivations were classified in group I (no reactivation), group II (loads <1000 cp/mL) and group III (loads >1000 cp/mL). CMV, EBV, Herpes Simpex Virus, Varicella Zoster Virus, and AdV-reactivations were treated according to local guidelines. HHV6 was treated only when there was clinical suspicion of disease. Thirty-six HLA-identical and 22 HLA nonidentical grafts were transplanted of which 43 were bone marrow or peripheral blood stem cells grafts and 15 were cord blood (CB) grafts. Median follow-up of the patients was 15.5 (1-35) months. HHV6 reactivation occurred in 39 of 58 (67%) patients with 31 of 39 (80%) occurring within the first 30 days post-HSCT. In 26 of 58 (45%) patients (group III), HHV6 reactivation was significantly associated with higher nonrelapse mortality (P = .02), using multivariate Cox proportional hazard models and grade 2-4 acute GVHD (P = .03) and chronic GVHD (P = .05) in a multivariate logistic regression analysis. HHV6 reactivation is very common after HSCT in children and is associated with serious transplantation-related morbidity and mortality. Although the exact role of HHV6 reactivation after HSCT has to be elucidated, early detection and initiation of therapy might be of benefit.