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REVIEW ARTICLE

Current Role of Prospective Monitoring and Preemptive and Prophylactic Therapy for Human Herpesvirus 6 After Allogeneic Stem Cell Transplantation

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Human herpesvirus 6 (HHV-6) frequently reactivates after allogeneic stem cell transplantation (SCT). Most patients are asymptomatic and viremia often resolves without therapy; however, transplant-related complications may be associated with reactivation. Multiple presentations have been attributed to HHV-6 reactivation after SCT including encephalitis. Several strategies have been trialed to reduce such risks or complications. Challenges exist with prospective monitoring strategies, and established thresholds of high-level reactivation may be limited. Three published guidelines and extensive trials focusing on preemptive and prophylactic strategies are reviewed. Future areas of investigation and high-risk populations are described. Existing trials and testing platforms have significant limitations, and to date no clear benefit for a preemptive or prophylactic intervention has been demonstrated.

Keywords. encephalitis; human herpesvirus-6; stem cell transplantation.

Human herpesvirus 6 (HHV-6) commonly reactivates after allogeneic stem cell transplantation (SCT), and in rare instances may cause disease. This β-herpesvirus was initially isolated in hematologic malignancy, but primary infection with genomic integration and immortalization occurs in nearly all individuals before adulthood [1–3]. Utilizing CD46 or CD134 receptors, the virus establishes lifelong integration at telomere regions in a variety of cells including peripheral blood mononuclear cells, monocytes, macrophages, bone marrow progenitor cells, and central nervous system (CNS) cells [4]. Additionally, 0.2%–2.9% of the population has chromosomal integration of HHV-6 (ciHHV-6) through Mendelian inheritance [4, 5]. As such, HHV-6 DNA, often at high levels $>10^6$ copies/mL, particularly in whole blood or cellular samples, may be persistently detected in the absence of any symptoms [5]. This proposed threshold remains limited by a lack of validation or standardization across testing platforms. Levels may be lower in cell-free samples, such as plasma, but remain persistently elevated in ciHHV6. HHV-6A and HHV-6B are 2 distinct viruses; however, nearly all cases of reactivation and clinical disease after allogeneic SCT are attributable to HHV-6B [4–7]. While antibody-based serologic testing and some commercial polymerase chain reaction (PCR) tests may not distinguish between HHV-6A and HHV-6B, detection of HHV-6A DNA in patients after allogeneic SCT should prompt an evaluation for ciHHV-6 [5–7]. Evaluation for ciHHV-6 may be performed with droplet digital PCR or fluorescence in situ hybridization of telomeric integration sites but is not routinely performed in most diagnostic laboratories [7]. In the studies discussed, HHV-6 DNA when detected or reported is most likely HHV-6B; however, many utilized testing platforms that do not differentiate between HHV-6A or HHV-6B. After allogeneic SCT, reactivation occurs in 30%–80% of patients, usually within the first 2–6 weeks, and has been associated with delayed monocyte engraftment, platelet engraftment, all-cause mortality, and grade III/IV acute graft-vs-host disease (aGVHD) [8–11]. A direct causal relationship between HHV-6 reactivation and delayed engraftment has not been established. Spontaneous resolution of HHV-6 viremia is common often within 3 weeks of onset [8, 12, 13]. While reactivation may correlate with delayed platelet recovery, an association with delayed neutrophil recovery has not clearly been established [8, 13–15]. Established risk factors for reactivation include human leukocyte antigen (HLA)–mismatched transplants, low recipient pretransplant anti–HHV-6 serologic titers, and umbilical cord blood transplant (CBT) [11, 16]. These, along with corticosteroid use, anti–T-cell monoclonal antibody use, higher grades of aGVHD, and myeloablative conditioning, are risk factors for HHV-6B

Received 05 May 2022; editorial decision 29 July 2022; accepted 01 August 2022; published online 3 August 2022

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Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac398

encephalitis [7, 9, 11, 16, 17]. Pneumonitis, hepatitis, myelitis, fever, rash, and myelosuppression have been attributed to HHV-6 reactivation after SCT or cellular therapy, but often alternative etiologies are present and should be ruled out [8, 9, 18–20]. The most feared and defined syndrome is a posttransplant limbic encephalitis comprised of anterograde amnesia, temporal lobe seizures, and/or enhancement of the uncus, amygdala, or hippocampus on magnetic resonance imaging [9, 21, 22]. Radiographic or clinical evidence of limbic system involvement is not required, though, and not seen in many patients with HHV-6B encephalitis.

HIGH-LEVEL HHV-6 REACTIVATION

Previous studies correlated high levels of plasma HHV-6 DNA with CNS disease or increased mortality with a proposed cutoff of $\geq 10^4$ copies/mL as high-level reactivation [8, 9, 11, 12, 14, 15]. This is limited by a lack of validation of such a threshold or standardization among commercially available assays. Compounding the issue, testing platforms may produce discordant results even in at-risk patients presenting with compatible syndromes [23]. Later studies show that HHV-6B encephalitis occurs even absent of high-level plasma DNA reactivation [23–25]. Detection of HHV-6 DNA in cerebrospinal fluid (CSF) may occur in a substantial portion of SCT patients without CNS dysfunction or with dysfunction due to an alternative etiology [25]. Treatment of such patients did not significantly change outcomes. Detection of HHV-6 DNA in plasma or CSF alone is insufficient for diagnosis of HHV-6 disease given how commonly reactivation occurs following allogeneic SCT, and alternative etiologies should be evaluated and ruled out prior to diagnosing HHV-6–related disease. High levels or persistently detectable HHV-6 DNA can suggest ciHHV-6 and should be evaluated if the diagnosis is unclear to avoid unnecessary or potentially harmful treatments [5, 26]. In prospectively monitored high-risk CBT, high-level reactivation has not been shown to be associated with poor outcomes including engraftment time, day 100 grade II–IV aGVHD, transplant-related mortality, or 1-year disease-free survival, and treatment of such patients did not alter outcomes [13]. Treatment when undertaken must be carefully considered, particularly if a benefit is unclear.

CURRENT CLINICAL PRACTICE GUIDELINES AND THERAPIES

Two clinical practice guidelines, from the Japan Society for Hematopoietic Cell Transplantation (JSHCT) and the European Conference on Infections in Leukaemia (ECIL), are published regarding HHV-6 disease in SCT. While the JSHCT guideline focuses primarily on HHV-6B encephalitis, the ECIL guideline notes that associations with disease states outside of encephalitis or fever with rash are only based on moderate or weak evidence [7, 26]. With rash alone, alternative etiologies are often more likely. In a study of transplant recipients with rash and HHV-6 reactivation, every single patient was diagnosed with aGVHD on histopathology and no HHV-6 antigen was detectable by immunostaining on samples on which it was performed [8]. An additional guideline published by the American Society for Transplantation and Cellular Therapy includes recommendations for HHV-6B specifically after CBT [27]. First-line therapies include ganciclovir and foscarnet. While these agents and cidofovir all have in vitro and in vivo activity against the virus, cidofovir is considered second line due to poor CNS penetration [7, 26, 28]. When initiated for treatment, maximum dosing should be given due to improved outcomes compared to reduced dosing regimens [26, 29]. In patients with HHV-6B encephalitis, a retrospective analysis demonstrated a reduction in 30-day all-cause mortality in patients receiving foscarnet, either alone or in combination; however, no clear significant difference was noted in patients treated with monotherapy ganciclovir compared to monotherapy foscarnet [29]. In the JSHCT guideline, foscarnet is therefore recommended (weak recommendation) as first-line therapy [26]. In vitro studies of human astroglioma cells demonstrated a reduced antiviral activity of ganciclovir in HHV-6A–infected cells not seen in HHV-6B–infected cells [30]. The clinical significance is unclear; as noted nearly all cases of HHV-6 reactivation after SCT are due to HHV-6B, and HHV-6A has not been causally linked to disease in this population [5–7]. Combination therapy with foscarnet and ganciclovir may be associated with reduced long-term neurologic sequelae, but no mortality benefit has been demonstrated, and guidelines only recommend consideration in severe cases [26, 31]. No randomized clinical trials exist for treatment of HHV-6B encephalitis. The duration of treatment is unclear. Guidelines recommend at least 3 weeks, and an extension of therapy until either HHV-6 DNA is undetectable in plasma and CSF and symptoms have improved [7, 26]. Refractory cases occur despite combination therapy and cidofovir may be trialed; however, there are no specific evidence or guideline recommendations in such situations. A comprehensive review for alternative etiologies should be undertaken. Even with appropriate therapy, outcomes may be poor and long-term neurologic sequelae common [10, 11, 26, 29, 31]. Comparisons of the 3 guidelines are available in Table 1. Where available, strength of recommendation is made based on the European Society of Clinical Microbiology and Infectious Diseases grading system for the ECIL guideline and the Grading of Recommendations Assessment, Development and Evaluation methodology for the JSHCT guideline.

PREEMPTIVE STRATEGIES

Due to poor outcomes of HHV-6B encephalitis, preemptive and prophylactic strategies have been attempted without significant success. Preemptive monitoring of HHV-6 DNA has

Table 1. Comparison of Guideline Recommendations for Human Herpesvirus 6B DNA Monitoring and Therapy

Population	ECIL, 2019 Allogeneic SCT	JSHCT, 2019 Allogeneic SCT[a]	ASTCT, 2021 CBT[b]
Accepted risk factors for HHV-6B encephalitis	CBT, T-cell depleted allografts, unrelated donor or mismatched donor, aGVHD grades II–IV, glucocorticoid therapy	CBT, male sex, unrelated donor or mismatched donor, corticosteroid therapy, pre-engraftment syndrome, engraftment syndrome, aGVHD	Not discussed
Potential risk factors for HHV-6B encephalitis	Haploidentical transplant, pre-engraftment syndrome	Haploidentical transplant	Not discussed
When to test for ciHHV-6	No indication for routine testing; consider if unclear	1–10 × 10^6 copies/mL in whole blood or persistent DNA in plasma or serum (strong)	>10^5 copies/mL in whole blood or viremia unresponsive to therapy
Treatment	• Foscarnet 90 mg/kg q12h OR ganciclovir 5 mg/kg q12h (AIIu) • Combination therapy may be considered (CIII)	• Primary: foscarnet 60 mg/kg q8h or 90 mg/kg q12h (weak) • Secondary: ganciclovir 5 mg/kg q12h (weak) • Combination therapy in severe cases (weak)	Not discussed
Duration of therapy	At least 3 weeks with clearance of DNA from blood and, if possible, CSF (CIII)	At least 3 weeks with clearance of DNA from blood and, if possible, CSF (weak)	Not discussed
Prospective monitoring	Not recommended (DIIu)	Not recommended (weak)	Can be considered, no evidence to support; alternatively, as clinically indicated
Prophylactic therapy	Not recommended (DIIu)	Not recommended (weak)	Not recommended
Preemptive therapy	Not recommended (DIIu)	No recommendation No benefit to predict or prevent HHV-6B encephalitis	Can consider for high-level viremia Note no established threshold or evidence to support role[c]
Notes	No recommendation for treatment of end-organ disease outside of encephalitis (insufficient data)	Can consider biweekly monitoring during weeks 2–6 after CBT (expert opinion), but not for use for preemptive therapy	Note some centers prospectively monitor to day 60, but no evidence to support

Abbreviations: aGVHD, acute graft-vs-host disease; AIIu, Strongly supports a recommendation for use, based on evidence from at least one uncontrolled trial or from cohort- or case-control analytic studies; ASTCT, American Society for Transplantation and Cellular Therapy; CIII, Marginally supports a recommendation for use, expert opinion; CBT, cord blood transplant; ciHHV-6, chromosomally integrated human herpesvirus 6; CSF, cerebrospinal fluid; DIIu, Supports a recommendation against use, based on evidence from at least one uncontrolled trial or from cohort- or case-control analytic studies; ECIL, European Conference on Infections in Leukaemia; HHV-6B, human herpesvirus 6B; JSHCT, Japan Society for Hematopoietic Cell Transplantation; q8h, every 8 hours; q12h, every 12 hours; SCT, stem cell transplant.

[a]Specific to HHV-6B encephalitis.

[b]Guideline for infection prophylaxis after CBT, not specific to HHV-6B.

[c]Refers to ECIL guideline for preemptive therapy, which explicitly recommends against preemptive therapy.

several challenges. HHV-6 DNA rises rapidly and suddenly around the onset of symptoms in patients with HHV-6B encephalitis [8, 10, 32, 33]. Due to viral kinetics, the high incidence of asymptomatic HHV-6 reactivation after SCT, and the limitations with current testing platforms, there is no established role for HHV-6 preemptive monitoring to prevent HHV-6B encephalitis. In preemptive treatment studies, foscarnet is more frequently utilized, rather than ganciclovir, due to concerns of myelosuppression [33, 34]. Multiple prospective and multicenter studies have found no benefit from preemptive strategies, and the majority of patients developed some adverse event potentially attributable to foscarnet therapy [32, 33]. A lack of evidence supporting a specific threshold to initiate therapy further complicates preemptive strategies.

PROPHYLACTIC STRATEGIES

Prophylactic strategies have not fared better. In a small heterogeneous safety study of 20 patients, prophylactic foscarnet 90 mg/kg/day demonstrated non–statistically significant potential to reduce HHV-6B–related CNS dysfunction at a potential cost for a trend of increased side effects [35]. However, a larger prospective cohort analysis of 118 patients found no benefit of prophylactic foscarnet 50 mg/kg/day in preventing HHV-6 reactivation or HHV-6B encephalitis [36]. Specifically for high-risk double CBT, a retrospective secondary analysis found higher rates of HHV-6 reactivation in patients receiving sirolimus and mycophenolate mofetil compared to cyclosporine and mycophenolate mofetil [37]. Multivariate analysis showed that only HHV-6 reactivation before neutrophil recovery was associated with risk of graft failure. The study likely suffered from ascertainment bias as HHV-6 reactivation was not evaluated prospectively but only in response to symptoms, such as delayed engraftment, and a similar study of 125 double CBT patients with prospective monitoring found no such findings as well as a HHV-6 reactivation rate of 94% [13]. While the study suggests that sirolimus may be associated with HHV-6 reactivation, patients receiving sirolimus were

older and had fewer comorbid conditions, and the change occurred due to a change in institutional practice in 2012 and prospective monitoring of HHV-6 DNA was not performed. Further case-controlled or prospective studies with prospective monitoring of HHV-6 DNA would be required to confirm this association. A subsequent retrospective analysis of 25 CBT patients receiving foscarnet prophylaxis of 45 mg/kg twice daily failed to demonstrate a reduction in cumulative rates of HHV-6 reactivation, but did suggest higher rates of neutrophil engraftment and 6-month overall survival [38]. Unfortunately, prospective monitoring was only performed in the foscarnet prophylaxis group of this study and compared to a control population, which in part as previously discussed, did not have prospective monitoring and likely suffered from ascertainment bias [37, 38]. Additionally, donor type of single vs double CBT, HLA matching, total nucleated cell dose, and CD34 dose were significantly different between groups, making comparisons difficult [38]. Single CBT alone was associated with improved neutrophil engraftment compared to double CBT [38]. A larger prospective multicenter trial evaluated 57 patients receiving foscarnet prophylaxis of 90 mg/kg daily and found no difference in rates of HHV-6B encephalitis; moreover, a non–statistically significant trend toward more encephalitis occurred in the foscarnet arm [24]. The primary endpoint of lower rates of high-level HHV-6 reactivation, defined as $\geq 10^4$ copies/mL of HHV-6 DNA in plasma, was significant in the foscarnet prophylaxis arm; however, this only occurred at the week 3 and week 4 timepoints during the study and no difference in rates of HHV-6B encephalitis, grade II–IV aGVHD, or grade III/IV aGVHD were found [24]. Most (5/7) patients receiving prophylaxis who developed encephalitis did not have high-level HHV-6 reactivation. Overall survival and rates of graft failure were not evaluated between groups. Notably, 13 of 57 (23%) of patients were unable to complete 21 days of foscarnet prophylaxis, and of 3 of 57 (5.2%) developed acute kidney injury limiting therapy entirely [24]. Dose adjustment was required in 18.5% of overall foscarnet administrations due to renal dysfunction.

DISCUSSION AND FUTURE DIRECTIONS

Due to these studies, all 3 published guidelines either expressly recommend against routine prospective testing of HHV-6 DNA after allogeneic SCT, or limit it to a consideration for a short period after transplantation in only the highest-risk patients such as after CBT [7, 26, 27]. In such populations, published guidelines note consideration of a limited monitoring period of 2–6 weeks or 60 days following CBT, but acknowledge there is no current evidence of a benefit for preemptive or prophylactic therapy in these patients [26, 27]. Haploidentical transplantation may present an additional population with higher risk of HHV-6B encephalitis for which prospective studies are needed [39–41]. HHV-6 reactivation remains challenging in the allogeneic SCT setting and may be associated with significant complications such as delayed platelet engraftment, high-grade aGVHD, and HHV-6B encephalitis. Reactivation is common, particularly after CBT, and studies to date have not been able to reliably predict which patients are at highest risk of progression to HHV-6B encephalitis and disease, in part due to viral kinetics and limitations of current testing platforms. While earlier studies proposed a risk threshold for high-level HHV-6 DNA reactivation in plasma, current evidence suggests that disease, including HHV-6B encephalitis, may occur even in the absence of high-level plasma reactivation [23–25]. The potential for distinct HHV-6 reactivation in patients with ciHHV-6 has been considered but remains clinically controversial [7]. Testing platforms suffer from a lack of standardization in measurement of HHV-6 DNA levels, and discordance among platforms has been noted [23]. Additional populations, such as patients following chimeric antigen receptor T-cell therapy, may carry increased risks and require further evaluation [20, 23]. In unclear scenarios, ciHHV-6 should be evaluated, but is not yet standard of care in most transplant centers. Prospective monitoring and preemptive, and prophylactic therapy trials have not demonstrated a clear benefit for patient outcomes and pose significant potential drug toxicities with therapy that should be carefully considered by providers and transplant centers caring for such patients in the absence of HHV-6 disease.

Notes

Potential conflicts of interest. The author: No reported conflicts.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Salahuddin SZ, Ablashi DV, Markham PD, et al. Isolation of a new virus, HBLV, in patients with lymphoproliferative disorders. Science **1986**; 234:596–601.
2. Okuno T, Takahashi K, Balachandra K, et al. Seroepidemiology of human herpesvirus 6 infection in normal children and adults. J Clin Microbiol **1989**; 27:651–3.
3. Levy JA, Ferro F, Greenspan D, Lennette ET. Frequent isolation of HHV-6 from saliva and high seroprevalence of the virus in the population. Lancet **1990**; 335: 1047–50.
4. Aimola G, Beythien G, Aswad A, Kaufer BB. Current understanding of human herpesvirus 6 (HHV-6) chromosomal integration. Antiviral Res **2020**; 176: 104720.
5. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: questions and answers. Rev Med Virol **2012**; 22:144–55.
6. Ablashi D, Agut H, Alvarez-Lafuente R, et al. Classification of HHV-6A and HHV-6B as distinct viruses. Arch Virol **2014**; 159:863–70.
7. Ward KN, Hill JA, Hubacek P, et al. Guidelines from the 2017 European Conference on Infections in Leukaemia for management of HHV-6 infection in patients with hematologic malignancies and after hematopoietic stem cell transplantation. Haematologica **2019**; 104: 2155–63.
8. Ogata M, Kikuchi H, Satou T, et al. Human herpesvirus 6 DNA in plasma after allogeneic stem cell transplantation: incidence and clinical significance. J Infect Dis **2006**; 193:68–79.
9. Zerr DM, Corey L, Kim HW, et al. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis **2005**; 40: 932–40.
10. Ogata M, Satou T, Kadota J, et al. Human herpesvirus 6 (HHV-6) reactivation and HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter, prospective study. Clin Infect Dis **2013**; 57:671–81.

11. Hill JA, Koo S, Guzman Suarez BB, et al. Cord-blood hematopoietic stem cell transplant confers an increased risk for human herpesvirus-6–associated acute limbic encephalitis: a cohort analysis. Biol Blood Marrow Transplant **2012**; 18: 1638–48.
12. Ogata M, Satou T, Kawano R, et al. Correlations of HHV-6 viral load and plasma IL-6 concentration with HHV-6 encephalitis in allogeneic stem cell transplant recipients. Bone Marrow Transplant **2010**; 45:129–36.
13. Olson AL, Dahi PB, Zheng J, et al. Frequent human herpesvirus-6 viremia but low incidence of encephalitis in double-unit cord blood recipients transplanted without antithymocyte globulin. Biol Blood Marrow Transplant **2014**; 20:787–93.
14. Ljungman P, Wang FZ, Clark DA, et al. High levels of human herpesvirus 6 DNA in peripheral blood leucocytes are correlated to platelet engraftment and disease in allogeneic stem cell transplant patients. Br J Haematol **2000**; 111:774–81.
15. Dulery R, Salleron J, Dewilde A, et al. Early human herpesvirus type 6 reactivation after allogeneic stem cell transplantation: a large-scale clinical study. Biol Blood Marrow Transplant **2012**; 18:1080–9.
16. Yamane A, Mori T, Suzuki S, et al. Risk factors for developing human herpesvirus 6 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation and its association with central nervous system disorders. Biol Blood Marrow Transplant **2007**; 13:100–6.
17. Yoshikawa T, Asano Y, Ihira M, et al. Human herpesvirus 6 viremia in bone marrow transplant recipients: clinical features and risk factors. J Infect Dis **2002**; 185: 847–53.
18. Miyashita N, Endo T, Onozawa M, et al. Risk factors of human herpesvirus 6 encephalitis/myelitis after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis **2017**; 19:e12682.
19. Shiroshita K, Mori T, Kato J, et al. Clinical characteristics of human herpesvirus-6 myelitis after allogeneic hematopoietic stem cell transplantation and its favorable outcome by early intervention. Bone Marrow Transplant **2020**; 55:939–45.
20. Handley G, Khawaja F, Kondapi DS, et al. Human herpesvirus 6 myelitis after chimeric antigen receptor T-cell therapy. Int J Infect Dis **2021**; 112:327–9.
21. Wainwright MS, Martin PL, Morse RP, et al. Human herpesvirus 6 limbic encephalitis after stem cell transplantation. Ann Neurol **2001**; 50:612–9.
22. Seeley WW, Marty FM, Holmes TM, et al. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology **2007**; 69:156–65.
23. Handley G, Hasbun R, Okhuysen P. Human herpesvirus 6 and central nervous system disease in oncology patients: a retrospective case series and literature review. J Clin Virol **2021**; 136:104740.
24. Ogata M, Takano K, Moriuchi Y, et al. Effects of prophylactic foscarnet on human herpesvirus-6 reactivation and encephalitis in cord blood transplant recipients: a prospective multicenter trial with an historical control group. Biol Blood Marrow Transplant **2018**; 24:1264–73.
25. Hill JA, Boeckh MJ, Sedlak RH, et al. Human herpesvirus 6 can be detected in cerebrospinal fluid without associated symptoms after allogeneic hematopoietic cell transplantation. J Clin Virol **2014**; 61:289–92.
26. Ogata M, Uchida N, Fukuda T, et al. Clinical practice recommendations for the diagnosis and management of human herpesvirus-6B encephalitis after allogeneic hematopoietic stem cell transplantation: the Japan Society for Hematopoietic Cell Transplantation. Bone Marrow Transplant **2020**; 55:1004–13.
27. Olsen AL, Politikos I, Brunstein C. Guidelines for infection prophylaxis, monitoring and therapy in cord blood transplantation. Transplant Cell Ther **2021**; 27: 359–62.
28. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. Clin Microbiol Rev **2015**; 28:313–35.
29. Ogata M, Oshima K, Ikebe T, et al. Clinical characteristics and outcome of human herpesvirus-6 encephalitis after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant **2017**; 52:1563–70.
30. Akyani N, Fotheringham J, Yao K, et al. Efficacy of antiviral compounds in human herpesvirus-6–infected glial cells. J Neurovirol **2006**; 12:284–93.
31. Toomey D, Phan TL, Nguyen V, et al. Retrospective case analysis of antiviral therapies for HHV-6 encephalitis after hematopoietic stem cell transplantation. Transpl Infect Dis **2021**; 23:e13443.
32. Ogata M, Satou T, Kawano R, et al. Plasma HHV-6 viral load-guided preemptive therapy against HHV-6 encephalopathy after allogeneic stem cell transplantation: a prospective evaluation. Bone Marrow Transplant **2008**; 41: 279–85.
33. Ishiyama K, Katagiri T, Hoshino T, et al. Preemptive therapy of human herpesvirus-6 encephalitis with foscarnet sodium for high-risk patients after hematopoietic SCT. Bone Marrow Transplant **2011**; 46:863–9.
34. Wang H, Zhu L, Xue M, et al. Low-dose foscarnet preemptive therapy for cytomegalovirus viremia after haploidentical bone marrow transplantation. Biol Blood Marrow Transplant **2009**; 15:519–20.
35. Ishiyama K, Katagiri T, Ohata K, et al. Safety of pre-engraftment prophylactic foscarnet administration after allogeneic stem cell transplantation. Transpl Infect Dis **2012**; 14:33–9.
36. Ogata M, Satou T, Inou Y, et al. Foscarnet against human herpesvirus (HHV)-6 reactivation after allo-SCT: breakthrough HHV-6 encephalitis following antiviral prophylaxis. Bone Marrow Transplant **2013**; 48:257–64.
37. Bejanyan N, Rogosheske J, DeFor TE, et al. Sirolimus and mycophenolate mofetil as calcineurin inhibitor-free graft-versus-host disease prophylaxis for reduced-intensity conditioning umbilical cord blood transplantation. Biol Blood Marrow Transplant **2016**; 22:2025–30.
38. El Jurdi N, Rogosheske J, DeFor J, et al. Prophylactic foscarnet for human herpesvirus 6: effect on hematopoietic engraftment after reduced-intensity conditioning umbilical cord blood transplantation. Transplant Cell Ther **2021**; 27: 84.e1–5.
39. Crocchiolo R, Giordano L, Rimondo A, et al. Human herpesvirus 6 replication predicts cytomegalovirus reactivation after allogeneic stem cell transplantation from haploidentical donor. J Clin Virol **2016**; 84:24–6.
40. Sisinni L, Gasior M, de Paz R, et al. Unexpected high incidence of human herpesvirus-6 encephalitis after naive T cell-depleted graft of haploidentical stem cell transplantation in pediatric patients. Biol Blood Marrow Transpl **2018**; 24:2316–23.
41. Greco R, Crucitti L, Noviello M, et al. Human herpesvirus 6 infection following haploidentical transplantation: immune recovery and outcome. Biol Blood Marrow Transpl **2016**; 22:2250–5.