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Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

Running title: HHV-6 encephalitis in allo-HSCT

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Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

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38 **Abstract**

39 **Background:** Human herpesvirus 6 (HHV-6) encephalitis is a known life-threatening
40 complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT).
41 However, few studies have focused on the occurrence of HHV-6 encephalitis in patients
42 receiving mycophenolate mofetil (MMF) combined with a calcineurin inhibitor as
43 prophylaxis for graft-versus-host disease (GVHD). This study aimed to investigate the
44 impact of MMF administered for GVHD prophylaxis in the occurrence of HHV-6
45 encephalitis after allo-HSCT and the characteristics of this condition.

46 **Methods and Results:** We retrospectively analyzed 73 patients who underwent
47 allo-HSCT (83 transplants) at our hospital between April 2010 and December 2015.
48 MMF (2–3 g/day) was administered along with a calcineurin inhibitor. Seven patients
49 (8.0%) developed encephalitis due to HHV-6. The median period from allo-HSCT to
50 the onset of HHV-6 encephalitis was 23 days (range, 17–98 days). The cumulative
51 incidence of HHV-6 encephalitis on day 100 after treatment was 12% and 6% in
52 patients who underwent cord blood transplantation (CBT) and non-CBT (i.e., bone
53 marrow transplantation and peripheral blood stem cell transplantation), respectively (P
54 = 0.344). Neurological symptoms of encephalitis were more severe in non-CBT cases
55 than those in CBT cases. All patients diagnosed with HHV-6 encephalitis were treated

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

56 with ganciclovir or foscarnet. None of the enrolled patients died from HHV-6

57 encephalitis.

58 **Conclusions:** MMF may have the potential to increase the frequency of severe HHV-6

59 encephalitis in patients undergoing CBT and non-CBT. Thus, MMF should be

60 administered with caution, and patients should be monitored closely for HHV-6

61 encephalitis even those who did not undergo CBT.

62

63 **Key words:** allogeneic hematopoietic stem cell transplantation, HHV-6, encephalitis,

64 mycophenolate mofetil

65

66 **Introduction**

67 Human herpes virus 6 (HHV-6), which includes HHV-6A and HHV-6B, belongs to
68 Roseolaviruses, although HHV-6A and HHV-6B are today considered as two different
69 species. HHV-6B causes exanthema subitum and is mostly reactivated after allogeneic
70 hematopoietic stem cell transplantation (allo-HSCT). HHV-6 reactivation occurs in
71 approximately 50% of allo-HSCT recipients^[1,2] and often occurs 0–9 days after
72 neutrophil engraftment. The peak viral load is observed approximately 3–4 weeks after
73 allo-HSCT^[1,2].

74 HHV-6 can cause skin rash, interstitial pneumonia, encephalitis, and
75 myelosuppression, among other conditions^[3-7]. Particularly, encephalitis caused by
76 HHV-6 can be fatal. HHV-6 encephalitis typically develops during the early
77 engraftment period at approximately 18–24 days after allo-HSCT^[1,8-10]. HHV-6
78 encephalitis starts with damage to the cerebral limbic system including the hippocampus,
79 followed by the development of symptoms that typically include disturbed
80 consciousness, impaired short-term memory, and seizures. HHV-6 encephalitis is
81 reported more frequently in cases of cord blood transplantation (CBT) than in cases of
82 non-CBT, i.e., bone marrow transplantation (BMT) and peripheral blood stem cell
83 transplantation (PBSCT)^[8,11-16].

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

84 Mycophenolate mofetil (MMF) is an immunosuppressive drug used as prophylaxis
85 for graft-versus-host disease (GVHD). Viral infection develops more frequently in
86 patients who have received MMF than in those who have received short-term
87 methotrexate (MTX)^[17]. The incidence of HHV-6 encephalitis in patients receiving
88 MMF is unclear. This study aimed to investigate the impact of MMF administered for
89 GVHD prophylaxis in the occurrence of HHV-6 encephalitis after allo-HSCT and the
90 characteristics of this condition.

91

Patients and Methods

This retrospective study was conducted at Kobe University Hospital and included patients who met the following inclusion criteria: (i) age $\geq$ 18 years; (ii) presence of a hematological disease; (iii) administered MMF for GVHD prophylaxis; and (iv) patients who underwent allo-HSCT at our hospital between March 2010 and September 2015. MMF was used in combination with a calcineurin inhibitor for GVHD prophylaxis. MMF was administered for 30 days from the day of transplantation at a dose of 1,000 mg every 8 hours (3,000 mg per day) for those who had undergone BMT and PBSCT and 1,000 mg every 12 hours (2,000 mg per day) for those who had undergone CBT. After 30 days, we tapered the dose of MMF every 7 days, according to institutional protocol (Figure 1) ^[18].

Clinical information, including patient background, condition of transplantation (donor, graft source, conditioning regimen, and GVHD prophylaxis), clinical course, and clinical outcomes, were collected from medical records. HHV-6 encephalitis was diagnosed based on clinical manifestation of encephalitis, such as disturbed consciousness and epilepsy, and the HHV-6 viral titer assessed via real-time polymerase chain reaction (PCR) analysis of the cerebrospinal fluid (CSF) sample obtained via lumbar puncture. The HHV-6 primers and probe setting were previously described ^[19,20].

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

Brain magnetic resonance imaging (MRI) was performed to rule out posterior reversible encephalopathy syndrome.

This study was approved by the ethics committees of Kobe University and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Clinical data consisted of age at transplantation, sex, primary disease, disease status, stem cell source, human leucocyte antigen (HLA) mismatch, conditioning regimens, transfused cell count, laboratory findings, course of transplantation therapy, and outcomes.

We compared categorical and continuous variables using the Fisher's exact test and the Mann-Whitney U-test, respectively. Cumulative incidence curves were used in competing risks setting, with death treated as a competing event, to calculate the probability of HHV-6 encephalitis. All statistical tests were 2-sided, and the significance level was set at 0.05. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)^[21]. More

precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics

A total of 73 patients (83 transplants) underwent allo-HSCT with MMF administered for GVHD prophylaxis between April 2010 and December 2015. A total of 33 cases of CBT were performed, while non-CBT was performed in 50 cases (39 BMT cases, and 11 PBSCT cases). The patient characteristics are shown in Table 1. The cohort comprised predominantly male patients at a male-to-female ratio of 44:29. Acute myeloid leukemia was the most common underlying disease in our cohort ($n = 41$), followed by acute lymphoblastic leukemia ($n = 14$). The proportion of unrelated transplantation, myeloablative conditioning, and cases using tacrolimus (TAC) for GVHD prophylaxis was significantly different between the CBT and non-CBT cases.

In all cases, acyclovir or valacyclovir was administered from 7 days before allo-HSCT for prophylaxis against herpes simplex virus and varicella zoster virus infection. Prophylactic anti-viral therapy against HHV-6 was not provided in any case. Only one patient (case 5), who presented with late onset HHV-6 infection 98 days after

transplantation, had received ganciclovir (GCV) and foscarnet (FCN) for

cytomegalovirus reactivation prior to the onset of HHV-6 encephalitis.

Incidence of HHV-6 encephalitis

Seven patients developed HHV-6 encephalitis. The overall cumulative incidence of HHV-6 encephalitis at 100 days after transplantation was 8.4% (95% CI: 3.7%–15.7%; Figure 2a). The cumulative incidences of HHV-6 encephalitis in patients who had undergone CBT and non-CBT were 12.1% (4/33 cases, 95% CI: 3.7%–25.8%) and 6% (3/50 cases, 95% CI: 1.5%–15%), respectively ($P = 0.344$, Figure 2b). The incidence of HHV-6 encephalitis was not statistically different between those who underwent BMT (7.7% [3/39 cases], 95% CI: 1.9%–18.8%), PBSCT (0% [0/11 cases]), and CBT (12.1% [4/33 cases], 95% CI: 3.7%–25.8%) ($P = 0.459$). In a subgroup analysis of unrelated transplantation cases with myeloablative conditioning, where TAC was administered for GVHD prophylaxis, the cumulative incidence of HHV-6 encephalitis was not significantly different between those who underwent CBT and non-CBT (18.2% vs. 16.7%, $P = 0.974$; Figure 2c).

Table 2 presents the details for the 7 cases of HHV-6 encephalitis. All 7 patients were male, had received one or two loci-mismatched HLA transplant, and underwent

allo-HSCT for the first time. Moreover, 5 of the 7 patients had received myeloablative conditioning (MAC) (i.e., CY/TBI [cyclophosphamide and total body irradiation] regimen regimen). Among the 34 patients who received the CY/TBI regimen, the cumulative incidence of HHV-6 encephalitis was 14.7% (5/34), which was higher than the overall cumulative incidence. The median onset of HHV-6 encephalitis was 23 days (range, 17–98 days) after allo-HSCT, which was just after neutrophil engraftment. A total of 3 of the 7 patients had received steroid treatment for engraftment syndrome.

Laboratory imaging findings

At the onset of HHV-6 encephalitis, the median CSF protein level was 50 mg/dL (range, 30–384 mg/dL), which was normal or moderately elevated, while the median CSF cell count was 5/mm³ (range, 1–75/mm³), which was normal or modestly elevated. The HHV-6 viral loads in CSF varied from case to case, but no significant differences were noted between BMT cases and CBT cases (Table 2). Although we performed brain MRI immediately after the onset of encephalitis to rule out posterior reversible encephalopathy syndrome, 6 of the 7 patients did not show any noteworthy abnormal signs. One case (case 3) showed abnormal MRI findings, which was an abnormal signal in the hippocampus. None of the patients had abnormal changes in the occipital lobes of

the cerebrum. However, we noted abnormal findings of HHV-6 encephalitis during the follow-up MRI, which were conducted 1–2 weeks after the onset of encephalitis, in all cases.

Neurological symptoms

The neurological symptoms associated with HHV-6 encephalitis, including convulsions and disturbed consciousness, were more severe in patients who had undergone BMT than those in patients who had undergone CBT. All 3 patients who developed HHV-6 encephalitis after BMT needed treatment with sedative agents and ventilators to manage convulsive seizures. By contrast, most patients who had undergone CBT and developed HHV-6 encephalitis could perform activities of daily living because the most common symptoms were only disturbed consciousness and short-term memory loss.

Two cases (cases 2 and 3) developed an autonomic storm, an excruciating autonomic dysfunction marked by a catecholamine surge, due to HHV-6-induced brain impairment, which made provision of general care difficult. Both patients had undergone BMT. Case 3 suddenly developed urinary retention 18 days after BMT. Concurrently, the patient experienced progression of disorientation, disturbed consciousness, and convulsion

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

within a few hours of the onset of urinary retention. FCN was administered on the same day that we suspected HHV-6 encephalitis. Immediately after he was transferred to the intensive care unit for the management of convulsion, the patient's blood pressure increased, and hyperhidrosis also developed, which led to hypothermia (minimum body temperature, 31°C). In addition, the patient had experienced persistent diarrhea (≥ 10 times a day) due to regimen-related toxicity until the previous day, but the diarrhea suddenly stopped. Although urinary retention and constipation can also occur owing to cauda equina syndrome or spinal cord disorder, we thought that his symptoms were caused by central autonomic disturbance because his neurological symptoms, such as hyperhidrosis, did not coincide with the spinal dermatome. Although status epilepticus stopped after 2 days, disturbed consciousness, hypertension, hyperhidrosis, and failure of thermoregulation persisted for up to 3 months. Case 2 also developed disturbed consciousness, status epilepticus and severe autonomic symptoms, including hypertension, constipation, abnormal sweating, and thermoregulation failure due to HHV-6 encephalitis. He required long-term ventilator therapy, and his autonomic symptoms persisted for up to 1 year.

Treatment

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

217 All 7 patients with HHV-6 encephalitis were treated with an anti-viral drug (FCN or
218 GCV). The median duration of anti-viral therapy was 39 days (range, 14–68 days). After
219 anti-viral therapy, HHV-6 DNA in CSF was no longer detectable in all 7 cases (Figure
220 3). The median time to reach undetectable levels of viral DNA in the CSF was 24 days
221 (range 10–33). Although no patient experienced exacerbation or HHV-6
222 encephalitis-related mortality, one case (case 3) died due to HHV-6-related pneumonia
223 after recovering from HHV-6 encephalitis. The majority of patients recovered from their
224 symptoms without severe sequelae and returned to normal daily living, but patients who
225 developed severe autonomic dysfunction developed neurological sequelae, such as
226 disturbed consciousness and abnormal thermoregulation.

227

Discussion

We retrospectively analyzed patients diagnosed with HHV-6 encephalitis after allo-HSCT who had been treated with the combination of a calcineurin inhibitor and MMF for GVHD prophylaxis in our hospital to assess the characteristics of HHV-6 encephalitis in patients receiving MMF for GVHD prophylaxis after allo-HSCT.

The reported incidence of HHV-6 encephalitis after allo-HSCT range from 0.95%^[22] to 11.6%^[23]. This variability in HHV-6 incidence may be a result of the varying transplantation methods (e.g., conditioning regimens, stem cell sources, and GVHD prophylaxis). In a systematic review conducted by Scheurer, the overall incidence of HHV-6 encephalitis in CBT and non-CBT patients was 8.3% and 0.5%, respectively^[14]. In a study focused on the incidence of HHV-6 encephalitis confirmed via polymerase chain reaction testing of CSF in Japan, the overall incidence were 3%–6.5%^{[15],[24]}, 4.9%–15.4%^[24], and 0.7%–3.0%^[11,24] in all cases, CBT cases, and non-CBT cases, respectively. The recent report from Japan which was a large-scale retrospective analysis, revealed that the cumulative incidences of HHV-6 encephalitis 100 days after transplantation in all cases, BMT or PBSCT and CBT cases were 2.3%, 1.6% and 5.0%, respectively^[25]. The incidence rates in our cohort tend to be higher than those in previous reports. Given that short-term methotrexate as replacement for MMF has been

widely used for allo-HSCT patients in Japan, our study suggests that MMF could increase the risk of HHV-6 encephalitis in both BMT patients and CBT patients. This may be due to the strong immunosuppression that is a result of long-term exposure of lymphocytes to MMF. Recently, Miyashita et al. also suggested that MMF is a risk factor for HHV-6 encephalitis^[16]. However, all patients with HHV-6 encephalitis/myelitis who had received MMF for GVHD prophylaxis in that report had undergone CBT^[16]. Their non-CBT patients who had HHV-6 encephalitis/myelitis had not received MMF. In our study, we found that HHV-6 encephalitis with severe clinical courses occurred in cases of BMT receiving MMF. Our study is the first to suggest the possibility that MMF increases the incidence of severe HHV-6 encephalitis in non-CBT patients, particularly BMT patients.

Previous studies reported other risk factors for HHV-6 encephalitis aside from CBT, including engraftment syndrome^[26] and acute GVHD^[13,26]. Male sex is also reported as a risk factor for HHV-6 reactivation^[15], and notably, patients with HHV-6 encephalitis in our cohort were all male.

Limbic encephalitis causes autonomic storm, and HHV-6 can also cause viral myelitis. It is important to distinguish between central autonomic symptoms and neurological symptoms of myelitis when a patient shows diverse symptoms of HHV-6

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

encephalitis. In our cohort, we determined whether the symptoms were central autonomic symptoms or not, by referring to the spinal dermatome. The presence of autonomic symptoms as well as symptoms of encephalitis such as disturbed consciousness and status epilepticus makes systemic management challenging. In our study, the severity of encephalitis was not related to the HHV-6 viral load, possibly because the timing for obtaining CSF sample varied among cases. Interestingly, HHV-6 encephalitis was more severe in patients who had undergone BMT than that in patients who had undergone CBT. Although the responsible mechanism remains unclear, it might have been caused by the higher dosage of MMF received by BMT patients than that by CBT patients. Okamura et al. reported a higher incidence of cytomegalovirus reactivation after allo-HSCT in patients who received a higher dose of MMF than in those who received a lower dose of MMF^[18].

Properly validated treatments of HHV-6 encephalitis or efficacious strategies have not been established. Other than FCN and GCV, new antiviral components, such as brincidofovir^[27] and artesunate^[28], are promising. However, FCN and GCV are the only treatment options for HHV-6 infection available in Japan. In our cohort, all cases were treated with a single course of antiviral therapy (FCN or GCV) that yielded good clinical outcomes except for case 3. There was no difference in the virological response

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

to antiviral treatment between the CBT and non-CBT cases. Moreover, efficacious strategies for prevention of HHV-6 encephalitis have not yet been established^[29].

Our study has certain limitations, with the small number of cases included being the major limitation. More data need to be collected to validate our findings. In addition, standard diagnostic criteria for HHV-6 encephalitis is not established, and various clinical examinations were performed to diagnose encephalitis across studies. Hence, we could not compare our findings with that of previous studies. Additionally, if encephalitis is not suspected, the routine CSF examinations after allo-HSCT are not performed, and thus mild encephalitis may be missed.

In conclusion, the results of this retrospective study indicate that the combination of a calcineurin inhibitor and MMF for GVHD prophylaxis might increase the risk of severe HHV-6 encephalitis in cases of non-CBT, particularly BMT. Although GCV and FCN are effective against HHV-6 and lead to better survival, MMF should be administered with caution, and patients should be monitored closely for HHV-6 encephalitis, even in those who underwent non-CBT. Further investigations should be conducted to validate our findings.

References

1. 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.
2. Maeda Y, Teshima T, Yamada M, Harada M. Reactivation of human herpesviruses after allogeneic peripheral blood stem cell transplantation and bone marrow transplantation. *Leukemia & lymphoma* 2000;39:229-239.
3. Clark DA. Human herpesvirus 6 and human herpesvirus 7: emerging pathogens in transplant patients. *Int J hematol* 2002;2:246-252.
4. Singh N, Paterson DL. Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus. *Transplantation* 2000;69:2474-2479.
5. Carrigan DR, Drobyski WR, Russler SK, Tapper MA, Knox KK, Ash RC. Interstitial pneumonitis associated with human herpesvirus-6 infection after marrow transplantation. *Lancet* 1991;338:147-149.
6. Drobyski WR, Dunne WM, Burd EM, *et al.* Human herpesvirus-6 (HHV-6) infection in allogeneic bone marrow transplant recipients: evidence of a marrow-suppressive role for HHV-6 in vivo. *J Infect Dis* 1993;167:735-739.

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

- 317 7. Yoshikawa T, Asano Y, Ihira M, *et al.* Human herpesvirus 6 viremia in bone marrow
318 transplant recipients: clinical features and risk factors. *J Infect Dis* 2002;185:847-853.
- 319 8. Sakai R, Kanamori H, Motohashi K, *et al.* Long-term outcome of human
320 herpesvirus-6 encephalitis after allogeneic stem cell transplantation. *Biol Blood Marrow*
321 *Transplant* 2011;17:1389-1394.
- 322 9. Zerr DM. Human herpesvirus 6 and central nervous system disease in hematopoietic
323 cell transplantation. *J Clin Virol* 2006;37:S52-S56.
- 324 10. Muta T, Fukuda T, Harada M. Human herpesvirus-6 encephalitis in hematopoietic
325 SCT recipients in Japan: a retrospective multicenter study. *Bone Marrow Transplant*
326 2009;43:583-585.
- 327 11. Fujimaki K, Mori T, Kida A, *et al.* Human herpesvirus 6 meningoencephalitis in
328 allogeneic hematopoietic stem cell transplant recipients. *Int J hematol* 2006;84:432-437.
- 329 12. Cheng FW, Lee V, Leung WK, *et al.* HHV-6 encephalitis in pediatric unrelated
330 umbilical cord transplantation: a role for ganciclovir prophylaxis? *Pediatr Transplant*
331 2010;14:483-487.
- 332 13. Hill JA, Koo S, Guzman Suarez BB, *et al.* Cord-blood hematopoietic stem cell
333 transplant confers an increased risk for human herpesvirus-6-associated acute limbic
334 encephalitis: a cohort analysis. *Biol Blood Marrow Transplant* 2012;18:1638-1648.

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

- 335 14. Scheurer ME, Pritchett JC, Amirian ES, Zemke NR, Lusso P, Ljungman P. HHV-6
336 encephalitis in umbilical cord blood transplantation: a systematic review and
337 meta-analysis. *Bone Marrow Transplant* 2013;48:574-580.
- 338 15. Ogata M, Satou T, Kadota J, *et al.* Human herpesvirus 6 (HHV-6) reactivation and
339 HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter,
340 prospective study. *Clin Infect Dis* 2013;57:671-681.
- 341 16. Miyashita N, Endo T, Onozawa M, *et al.* Risk factors of human herpesvirus 6
342 encephalitis/myelitis after allogeneic hematopoietic stem cell transplantation. *Transpl*
343 *Infect Dis* 2017:e12682.
- 344 17. Hamad N, Shanavas M, Michelis FV, *et al.* Mycophenolate-based graft versus host
345 disease prophylaxis is not inferior to methotrexate in myeloablative-related donor stem
346 cell transplantation. *Am J Hematol* 2015;90:392-399.
- 347 18. Okamura A, Yamamori M, Shimoyama M, *et al.* Pharmacokinetics-based optimal
348 dose-exploration of mycophenolate mofetil in allogeneic hematopoietic stem cell
349 transplantation. *Int J hematol* 2008;88:104-110.
- 350 19. Tanaka N, Kimura H, Hoshino Y, *et al.* Monitoring four herpesviruses in unrelated
351 cord blood transplantation. *Bone Marrow Transplant* 2000;26:1193-1197.

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

- 352 20. Tachikawa R, Tomii K, Seo R, *et al.* Detection of herpes viruses by multiplex and
353 real-time polymerase chain reaction in bronchoalveolar lavage fluid of patients with
354 acute lung injury or acute respiratory distress syndrome. *Respiration* 2014;87:279-86.
- 355 21. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for
356 medical statistics. *Bone Marrow Transplant* 2013;48:452-458.
- 357 22. Hill JA, Boeckh MJ, Sedlak RH, Jerome KR, Zerr DM. Human herpesvirus 6 can be
358 detected in cerebrospinal fluid without associated symptoms after allogeneic
359 hematopoietic cell transplantation. *J Clin Virol* 2014;61:289-292.
- 360 23. Vu T, Carrum G, Hutton G, Heslop HE, Brenner MK, Kamble R. Human
361 herpesvirus-6 encephalitis following allogeneic hematopoietic stem cell transplantation.
362 *Bone Marrow Transplant* 2007;39:705-709.
- 363 24. Yamane A, Mori T, Suzuki S, *et al.* Risk factors for developing human herpesvirus 6
364 (HHV-6) reactivation after allogeneic hematopoietic stem cell transplantation and its
365 association with central nervous system disorders. *Biol Blood Marrow Transplant*
366 2007;13:100-106.
- 367 25. Ogata M, Oshima K, Ikebe T, *et al.* Clinical characteristics and outcome of human
368 herpesvirus-6 encephalitis after allogeneic hematopoietic stem cell transplantation. *Bone*
369 *Marrow Transplant* 2017;52:1563-1570.

Human Herpesvirus 6 Encephalitis in Patients Administered Mycophenolate Mofetil as Prophylaxis for Graft-versus-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation.

- 370 26. Ogata M, Satou T, Kawano R, *et al.* Correlations of HHV-6 viral load and plasma
371 IL-6 concentration with HHV-6 encephalitis in allogeneic stem cell transplant recipients.
372 *Bone Marrow Transplant* 2010;45:129-136.
- 373 27. Bonnafous P, Bogaert S, Godet AN, Agut H. HDP-CDV as an alternative for
374 treatment of human herpesvirus-6 infections. *J Clin Virol* 2013;56:175-176.
- 375 28. Milbradt J, Auerochs S, Korn K, Marschall M. Sensitivity of human herpesvirus 6
376 and other human herpesviruses to the broad-spectrum antiinfective drug artesunate. *J*
377 *Clin Virol* 2009;46:24-28.
- 378 29. Ogata M, Takano K, Moriuchi Y, *et al.* Effects of Prophylactic Foscarnet on Human
379 Herpesvirus-6 Reactivation and Encephalitis in Cord Blood Transplant Recipients: A
380 Prospective Multicenter Trial with an Historical Control Group. *Biol Blood Marrow*
381 *Transplant* 2018;24:1264-1273.

382

Figure legends

Fig. 1 Schedule of MMF administration

MMF, mycophenolate mofetil; BMT, bone marrow transplantation; PBSCT, peripheral blood cell transplantation; CBT, cord blood transplantation

Fig. 2 Cumulative incidence of HHV-6 encephalitis

The overall cumulative incidence was 8.4% (a), and the incidence was not significantly different between the CBT cases and non-CBT (BMT and PBSCT) cases (b)

Fig.3 Changes in HHV-6 viral loads

Viral loads had decreased rapidly after antiviral treatment in all 7 cases.

(GCV, ganciclovir; FCN, foscarnet)

Fig. 1

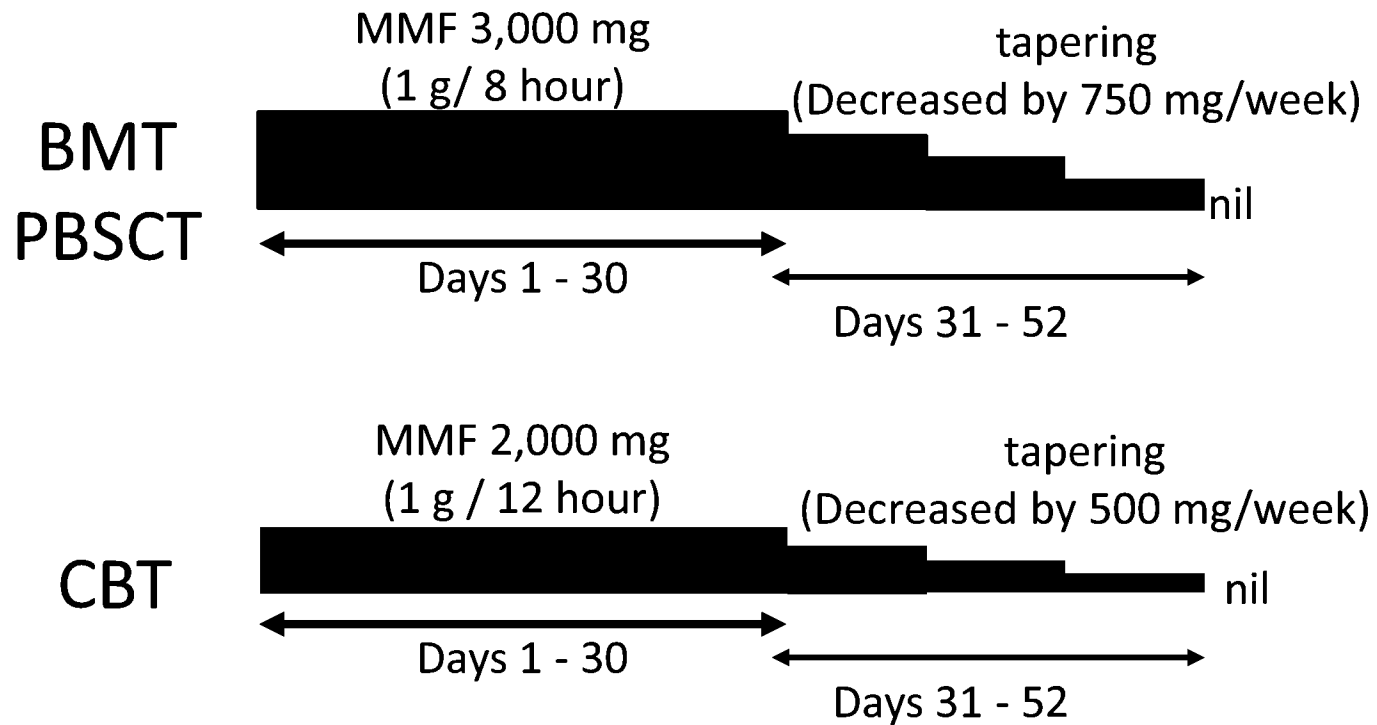
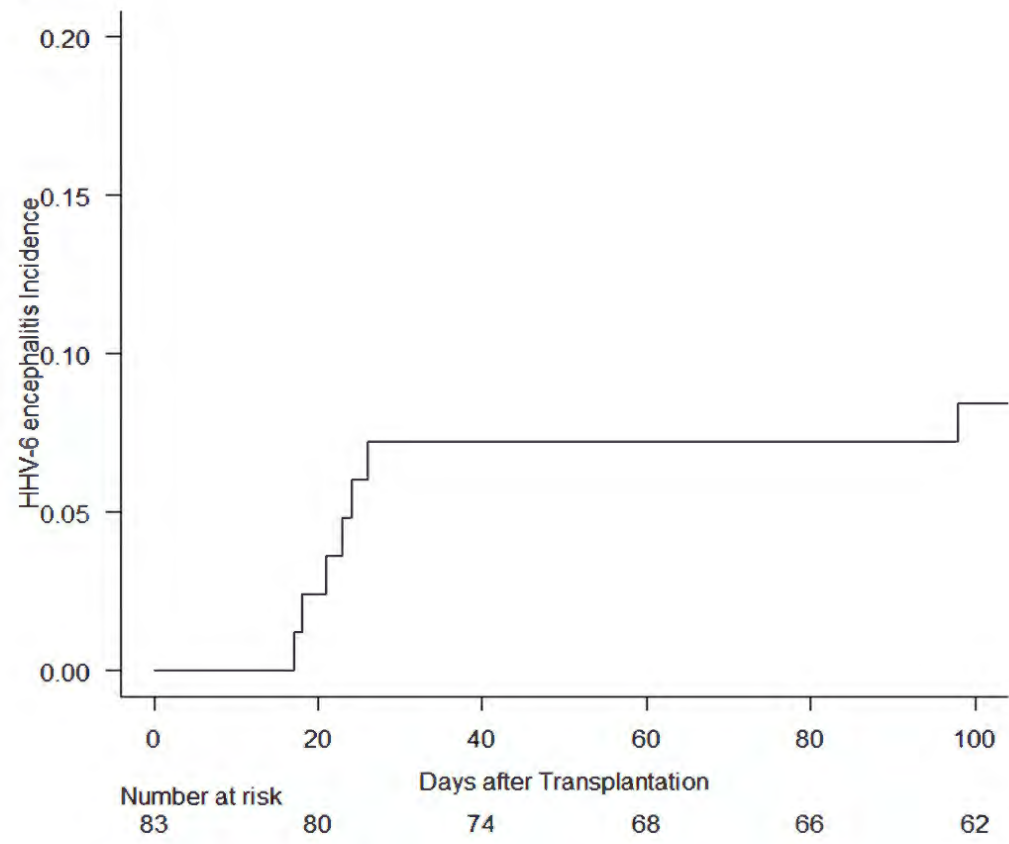


Figure 2

a.



b.

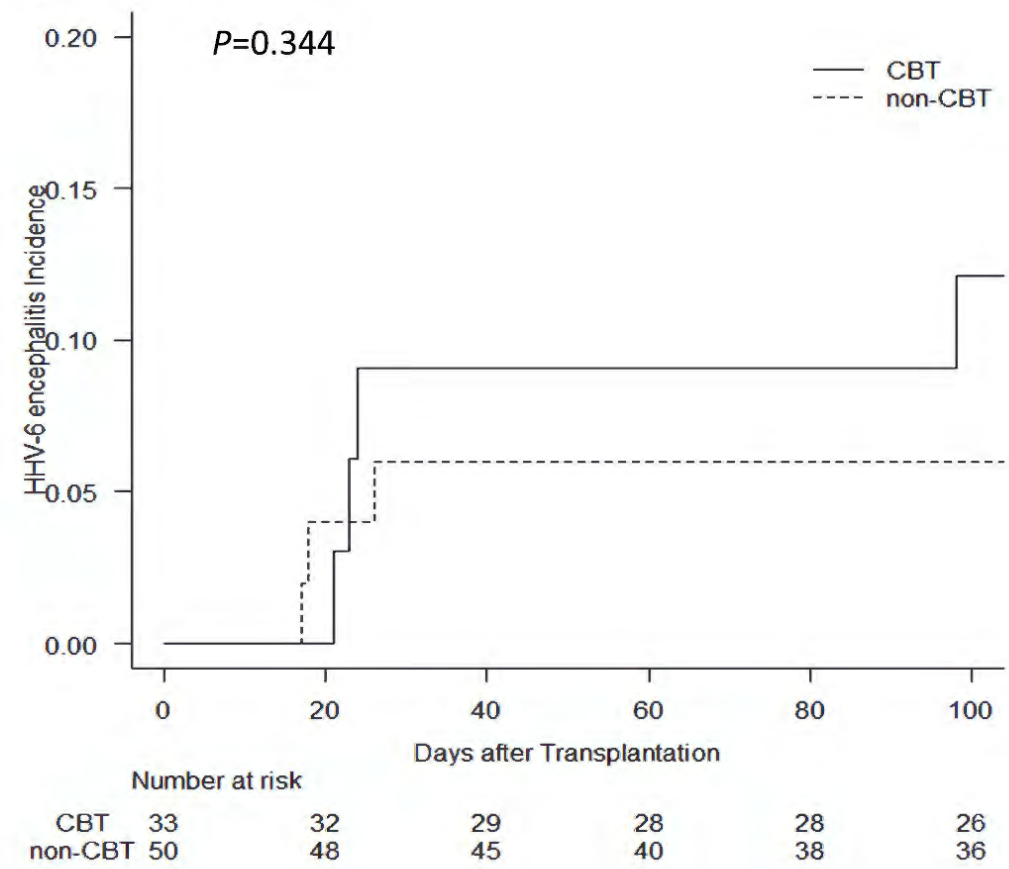


Fig.3

