LETTER TO THE EDITOR

Human herpesvirus-6 encephalitis in hematopoietic SCT recipients in Japan: a retrospective multicenter study

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Recently, increasing evidence suggests that human herpesvirus-6 (HHV-6) reactivated in the central nervous system (CNS) could play an important role in the pathogenesis of neurological symptoms. *In vitro*, HHV-6 may infect astrocytes, oligodendrocytes and neurons,^{1,2} and *in vivo*, HHV-6 was also detected in such cell types in an immunocompromised host.³ The first patient with fatal encephalitis during BMT was described in 1994.⁴ In the course of hematological SCT, the reactivation of HHV-6 in peripheral blood occurred at a rate of 17 to 70%,^{5–7} whereas the reactivation in cerebrospinal fluid associated with CNS symptoms occurred in only 5 (1.5%) of 338 BMT recipients.⁸ To date, the clinical entity of HHV-6 encephalitis has been established in patients with CNS symptoms and HHV-6 reactivation in the cerebrospinal fluid, and over 40 hematopoietic SCT (HSCT) recipients have been reviewed.⁹ The purpose of this study was to clarify the clinical characteristics of HHV-6 encephalitis in Japanese HSCT recipients. We collected data from 130 transplantation centers in a retrospective study. We analyzed adult patients with HHV-6 encephalitis undergoing allo-HSCT for hematological diseases from January 1999 to December 2003. The diagnostic criteria of HHV-6 encephalitis must be fulfilled regarding both the CNS symptoms and the detection of HHV-6 in cerebrospinal fluid. Other etiologies that may cause CNS impairment should be ruled out. Data were collected using a voluntary report form. Medical doctors reported cases of patients with encephalitis occurring after SCT, if calcineurin inhibitor-induced encephalopathy could be excluded and they were not infected with other pathogens such as herpes simplex, CMV or EBV. Most importantly, PCR methods should have been performed in such patients. This study did not involve patients whose cause of encephalitis could not be specified or who died too early for an adequate diagnosis. Transplantation was performed according to the protocol of each center. Prophylaxis against GVHD involved CYA or tacrolimus combined with MTX with or without corticosteroids. We conducted a survey of HHV-6 encephalitis in 5484 allo-SCT recipients. Twenty-three patients satisfied the criteria of HHV-6 encephalitis. The patient characteristics are summarized in Table 1. Regarding the pre-transplant status of the original diseases, half of the patients were refractory to the previous chemotherapy. Four patients had earlier undergone transplantation. There were 21 out of 23 patients who underwent transplantation

from an HLA-mismatched related donor, unrelated donor, and using cord blood, and only 2 out of 23 from HLA-identical sibling donors. BMT was performed in 13 out of the 23 patients, whereas 5 out of the 23 patients received PBSCs. The remaining five patients underwent transplantation using cord blood. Sixteen of the patients received TBI involving a myeloablative conditioning regimen. In the remaining seven patients, fludarabine-based non-myeloablative therapy was used. Most of the patients received tacrolimus for GVHD prophylaxis, which reflects the mismatched HLA nature of the donor sources. The

Table 1 Patients' characteristics

Age (years), median (range)	38 (18–63)
Sex	
Male	15
Female	8
Disease	
AML	8
ALL	6
Malignant lymphoma	5
Others (myelodysplastic syndrome, aplastic anemia, chronic myelogenous leukemia)	4
Disease status	
CR/chronic phase	11
Refractory/relapse	12
Previous transplantation	
Autologous PBSCT	2
Unrelated BMT	1
Cord blood transplantation	1
No previous transplantation	19
Donor type	
HLA-identical sibling	2
HLA-mismatched sibling	5
Mother or child	4
Unrelated BM	7
Cord blood	5
Source	
BM	13
PBSCs	5
Cord blood	5
Conditioning	
Myeloablative (TBI-based)	16
Reduced intensity (fludarabine-based)	7
GVHD prophylaxis	
Tacrolimus plus MTX	13
CYA plus MTX	4
CYA or tacrolimus without MTX	5
Tacrolimus plus methylprednisolone	1

Table 2 Features of HHV-6 encephalitis

Onset (day), median (range)	22 (12–614)
<i>Disturbance of consciousness</i>	
Japan Coma Scale 100–300	9
Japan Coma Scale 10–30	5
Japan Coma Scale 1–3	7
Japan Coma Scale 0	2
<i>Other symptoms</i>	
Loss of short-term memory	17
Convulsion	16
Fever	14
Hypoxia	5
Headache	3
Change of character	3
PCR analysis of cerebrospinal fluid (day), median (range)	24 (17–620)
<i>Type of PCR</i>	
Quantitative PCR	9
Qualitative PCR	14
<i>Subtype of HHV-6</i>	
Subtype B	9
Unknown (A or B)	14
<i>MRI</i>	
Abnormality of MRI	18
MRI not performed	5
<i>Treatment of antiviral</i>	
Gancyclovir only	12
Foscavir only	4
Gancyclovir → foscavir	5
Gancyclovir plus foscavir	2
<i>Other agents</i>	
γ-Globulin	13
Acyclovir	4
Vidarabine	1
Donor lymphocyte infusion	1
<i>Outcome of encephalitis</i>	
Full recovery	11
After effects of memory loss	10
Dead (sepsis or hypoxia)	2
<i>GVHD</i>	
Grade 0	3
Grade I	4
Grade II	6
Grades III–IV	10
<i>Survival</i>	
Alive	16
Dead	7
<i>Cause of death (n = 7)</i>	
Sepsis	3
GVHD	1
Pulmonary hemorrhage	1
Relapse of leukemia	1
Hypoxia	1

Abbreviations: HHV-6 = human herpesvirus-6; MRI = magnetic resonance imaging.

The Japan Coma Scale, used in this study, is scored as follows: 0 = alert, 1–3 = awake without stimulation, 10–30 = awake with stimulation, 100–300 = not awake with stimulation.¹⁰

clinical characteristics of HHV-6 encephalitis are summarized in Table 2. The median onset of symptoms was day 22. In 15 patients, encephalitis occurred within 7 days, around the timing of granulocyte engraftment. Four major symptoms were noted: disturbance of consciousness (91%), loss of short-term memory (74%), convulsion (70%) and fever (61%). Five patients had hypoxia and some required mechanical ventilation. Cerebrospinal fluid analysis revealed an elevated cell count (lymphocytic pleocytosis) in 10 out of 23 patients. PCR analysis of cerebrospinal fluid samples was performed using quantitative or qualitative methods.

The median amount of viral DNA was $3.3 (0.8–500) \times 10^3$ copies/ml. In the examined range, nine out of nine patients showed subtype B of HHV-6. In the 18 patients who underwent magnetic resonance imaging in the acute phase, T2-weighted images showed a strong signal in the hippocampus, temporal lobe or limbic systems. Just before the onset of encephalitis, 10 patients received acyclovir for herpes simplex virus prophylaxis, one received gancyclovir for CMV prophylaxis, and one was administered both acyclovir and foscavir for herpes simplex virus and CMV prophylaxis. Just before the onset of encephalitis, 12 patients had commenced immunosuppressive treatment with steroids against GVHD, 11 received methylprednisolone at more than 0.5 mg/kg. As for treatment, all patients received gancyclovir and/or foscavir. Two patients were treated with a combination of gancyclovir at a dose of 5 mg/kg and foscavir. Five patients were switched from gancyclovir to foscavir. As a result, two patients died early before recovery from encephalitis, whereas 21 patients recovered from encephalitis, 10 of whom showed the after-effects of short-term memory impairment. Acute GVHD occurred in seven patients, became aggravated after the onset of encephalitis in five patients, and was fatal in one patient.

Our study indicated that the characteristics of HHV-6 encephalitis occurring in Japanese HSCT recipients are similar to those of European and American recipients. The present results may be of value to the hematologists for the following reasons: The occurrence of HHV-6 encephalitis is rare, but if HSCT is performed using an alternative donor other than an HLA-matched sibling for relapsed/refractory leukemia, HHV-6 encephalitis must be considered. There is no effective prophylaxis or method to monitor HHV-6 encephalitis; suspicion based on the characteristic symptoms, rapid diagnosis using magnetic resonance imaging and quantitative PCR analysis of the cerebrospinal fluid, and the prompt administration of antiviral drugs are crucial for patient management. Acute GVHD may progress after onset of HHV-6 encephalitis. Rehabilitation for short-term memory disturbance must also be considered.

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