Prognostic Factors for Chronic Active Epstein-Barr Virus Infection

Hiroshi Kimura,1 Tsuneo Morishima,2 Hirokazu Kanegane,3 Shouichi Ohga,4 Yo Hoshino,5 Akihiko Maeda,6 Shosuke Imai,7 Motohiko Okano,8 Tomohiro Morio,9 Shigeru Tsuchiya,10 Akihiro Yachie,11 Shinsaku Imashuku,12 Keisei Kawa,13 Hiroshi Wakiguchi,5 and Members of the Japanese Association for Research on Epstein-Barr Virus and Related Diseases

1Department of Pediatrics, Nagoya University Graduate School of Medicine, and 2Department of Health Science, Nagoya University School of Medicine, Nagoya; 3Department of Pediatrics, Faculty of Medicine, Toyama Medical and Pharmaceutical University, Toyama; 4Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka; Departments of 5Pediatrics and 6Microbiology, Kochi Medical School, Kochi; 7Department of Pediatrics, Hokkaido University Graduate School of Medicine, Sapporo; 8Department of General Medicine, Tokyo Medical and Dental University, School of Medicine, Tokyo; 9Department of Pediatrics, Yokohama City University School of Medicine, Kanagawa; 10Institute of Development, Aging and Cancer, Tohoku University, Sendai; 11School of Health Sciences, Faculty of Medicine, Kanazawa University, Kanazawa; 12Kyoto City Institute of Health and Environmental Sciences, Kyoto; and 13Department of Pediatrics, Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan

Chronic active Epstein-Barr virus infection (CAEBV) is a high-mortality and high-morbidity disease. To clarify the prognostic factors, a national survey was performed in Japan, and data for 82 patients who met the criteria for CAEBV were analyzed. Of these 82 patients, 47 were alive and 35 had already died. Multivariate analysis revealed that thrombocytopenia and age at disease onset were correlated with mortality. The probability of 5-year survival was 0.45 for older patients (onset age, ≥8 years), 0.94 for younger patients (P<.001), 0.38 for patients with thrombocytopenia (platelet count <4 platelets/μL at diagnosis), and 0.76 for patients without thrombocytopenia (P = .01). Furthermore, patients with T cell infection by EBV had shorter survival times than patients with natural killer cell infection (probability of 5-year survival, 0.59 vs. 0.87; P < .009). Patients with CAEBV with late onset of disease, thrombocytopenia, and T cell infection had significantly poorer outcomes.

Received 12 August 2002; revised 12 November 2002; electronically published 28 January 2003.

Presented in part: 10th International Symposium on Epstein-Barr Virus and Associated Malignant Disease, Cairns, Australia, 16–21 July 2002 (abstract 127).

Reprints or correspondence: Dr. Hiroshi Kimura, Dept. of Pediatrics, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan (hkimura@med.nagoya-u.ac.jp).

The Journal of Infectious Diseases 2003; 187:527–33
© 2003 by the Infectious Diseases Society of America. All rights reserved. 0022-1899/2003/18704-0001$15.00

Epstein-Barr virus (EBV) is a ubiquitous virus; most individuals are infected with EBV by early adulthood. Primary EBV infection is usually asymptomatic but sometimes progresses to infectious mononucleosis, which resolves spontaneously after the emergence of EBV-specific immunity [1, 2]. EBV causes chronic infections in apparently immunocompetent hosts [1, 3]. Chronic active EBV infection (CAEBV) is characterized by chronic or recurrent infectious mononucleosis–like symptoms that persist for a long time and by an unusual pattern of anti-EBV antibodies [4, 5]. Patients with CAEBV have high virus loads in their peripheral blood [6]. CAEBV is a high-mortality, high-morbidity disease with life-threatening complications [7–11]. Recent studies have indicated that clonal expansion of EBV-infected T cells and NK cells plays a central role in the pathogenesis of CAEBV [6, 12].

Treatment regimens for CAEBV have not yet been established. Antiviral or immunomodulatory agents, such as acyclovir, ganciclovir, vidarabine, interferon-α, and interleukin-2, have been tested with limited success in patients with CAEBV. Immunochemotherapy that involves etoposide, steroids, and cyclosporin A has been proposed for use in patients with advanced CAEBV [13], although no evidence has been forthcoming on
Data collection. In January 2001, a questionnaire that was demonstrated that patients with T cell infection by EBV had bocytopenia were associated with prognosis. Furthermore, we regression analysis, we showed that age at disease onset and thrombocytopenia were associated with prognosis. Furthermore, we demonstrated that patients with T cell infection by EBV had shorter survival times than those with NK cell infection.

**PATIENTS AND METHODS**

**Data collection.** In January 2001, a questionnaire that was developed by the Japanese Association for Research on Epstein-Barr Virus and Related Diseases was sent to a total of 953 departments of hematology, pediatrics, dermatology, and otorhinolaryngology, to assess the number of patients with suspected CAEBV in Japan. These departments were chosen to encompass the majority of the tertiary medical facilities where patients with CAEBV undergo treatment. Respondents were asked to include both living and deceased patients who had been diagnosed with CAEBV after 1990. A total of 164 patients were reported (an effective response rate of 72%) deemed appropriate for further study were reported.

**Case definition.** CAEBV was defined according to the following criteria, which were modified slightly from those described elsewhere [5, 6, 10]: (1) illness ≥3 months duration (EBV-related illness or symptoms including fever, persistent hepatitis, extensive lymphadenopathy, hepatosplenomegaly, pancytopenia, uveitis, interstitial pneumonia, hydroa vacciniforme, and hypersensitivity to mosquito bites); (2) increased amounts of EBV or grossly abnormal levels of EBV antibodies. Patient positive for ≥1 factor in each category to be diagnosed with CAEBV: detection of EBV DNA in tissues or peripheral blood by Southern blot hybridization; EBV-encoded small RNA 1-positive cells in affected tissues or peripheral blood; >10^{-5} copies/µg EBV DNA in peripheral blood mononuclear cells [18]; and grossly abnormal levels of EBV antibodies [anti–viral capsid antigen (VCA) IgG titers ≥5120 or anti–early antigen (EA) IgG titers ≥640 [5]; and (3) No evidence of previous immunological abnormalities or other recent infection that might explain the observed condition.

All of the questionnaires were thoroughly reviewed by members of the Japanese Association for Research on Epstein-Barr Virus and Related Diseases. Patients in whom the presence of symptoms, complications, laboratory data at diagnosis, EBV-specific antibodies, virus load, EBV-infected cells, clonality of EBV, human immunodeficiency virus (HIV) serostatus, surface marker analysis on peripheral blood cells, cytogenetic study, lymphocyte mitogen response, HLA, applied therapies, and outcomes. EBV-infected cells were identified by use of either quantitative polymerase chain reaction (PCR) or in situ hybridization using fractionated cells [18]. The fractionation was performed either by use of electric or magnetic cell sorting [6]. The clonality of EBV was determined by means of Southern blotting, using a terminal-repeat probe [19]. A total of 118 patients (an effective response rate of 72%) deemed appropriate for further study were reported.

**Table 1. Presence of Epstein-Barr virus-associated antibodies at diagnosis of infection.**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>No. of tested patients</th>
<th>Patients with positive results of antibody testing</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCA-IgG</td>
<td>81</td>
<td>81 (100)</td>
<td>1280 (20–20,480)</td>
</tr>
<tr>
<td>VCA-IgA</td>
<td>57</td>
<td>35 (61)</td>
<td>40 (10–160)</td>
</tr>
<tr>
<td>VCA-IgM</td>
<td>62</td>
<td>11 (18)</td>
<td>10 (10–80)</td>
</tr>
<tr>
<td>EA-DR-IgG</td>
<td>70</td>
<td>64 (91)</td>
<td>320 (10–20,480)</td>
</tr>
<tr>
<td>EA-DR-IgA</td>
<td>45</td>
<td>22 (49)</td>
<td>20 (10–640)</td>
</tr>
<tr>
<td>EA-DR-IgM</td>
<td>16</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>EBNA</td>
<td>75</td>
<td>62 (83)</td>
<td>40 (10–1280)</td>
</tr>
</tbody>
</table>

**NOTE.** EA-DR, early antigens diffuse restricted; EBNA, Epstein-Barr virus nuclear antigens; NA, not applicable; VCA, viral capsid antigens.

the efficacy of such treatments. Recently, successful treatment of CAEBV by allogeneic bone marrow transplantation was reported [14–17]. However, hematopoietic stem cell transplantation constitutes a substantial risk to recipient patients. Therefore, transplantation is indicated only for patients with a poor prognosis.

The purpose of this study was to clarify the prognosis and prognostic factors for CAEBV, to facilitate better treatment choices. We performed a national survey of CAEBV in Japan and found 82 patients who met the criteria for CAEBV. Clinical and laboratory data were analyzed and compared between living and deceased patients with CAEBV. By using multivariate regression analysis, we showed that age at disease onset and thrombocytopenia were associated with prognosis. Furthermore, we demonstrated that patients with T cell infection by EBV had shorter survival times than those with NK cell infection.

**Table 2. Epstein-Barr virus (EBV) load in peripheral blood.**

<table>
<thead>
<tr>
<th>Specimen, method</th>
<th>No.</th>
<th>Median result (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mononuclear cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In situ hybridization,a %</td>
<td>22</td>
<td>3.1 (0.1–90)</td>
</tr>
<tr>
<td>Quantitative PCR,b copies/µg</td>
<td>32</td>
<td>10^{3} (10^{1.2}–10^{3.7})</td>
</tr>
<tr>
<td>White blood cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative PCR,b copies/µg</td>
<td>3</td>
<td>10^{2} (10^{3.2}–10^{4.4})</td>
</tr>
<tr>
<td>Plasma or serum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative PCR,b copies/mL</td>
<td>29</td>
<td>10^{9} (10^{2.5}–10^{9})</td>
</tr>
</tbody>
</table>

**NOTE.** a In situ hybridization was performed with the EBV-encoded small RNA 1 probe. b Quantitative polymerase chain reaction (PCR) was real-time PCR or competitive PCR.
In total, 82 patients with CAEBV (42 male and 40 female patients) were enrolled in this study. The age at the onset of disease ranged from 9 months to 53 years (mean, 11.3 years). Of the 82 patients, 47 were still alive after 8 months to 18 years of observation (mean, 6.4 years). Thirty-five patients (43%) had died, after survival periods that ranged from 5 months to 12 years after onset of CAEBV (mean, 4.3 years). Causes of death included transplantation-related complications (n = 7), malignant lymphoma (n = 6), hepatic failure (n = 3), hemophagocytic syndrome (n = 3), leukemia (n = 2), multiple organ failure (n = 2), unknown (n = 2), and other (n = 4). Sixteen patients had undergone hematopoietic stem cell transplantation. Eight of the 16 were alive after 4–41 months of remission. One patient relapsed and died shortly afterward. The other 7 patients died of transplantation-related complications, which were defined as complications that occurred within 60 days of transplantation and were considered to be associated with transplantation and not with the disease itself. The transplantation-related complications included sepsis (n = 2), veno-occlusive disease (n = 1), graft-versus-host disease (n = 1), thrombotic microangiopathy (n = 1), pneumonia (n = 1), and pulmonary edema (n = 1). There were no remarkable or common family or medical histories among the patients with CAEBV.

### Clinical and laboratory features.

The major signs and symptoms of patients with CAEBV were as follows: fever (92.7%), hepatomegaly (79.3%), splenomegaly (73.2%), liver dysfunction (67.1%), thrombocytopenia (45.1%), anemia (43.9%), lymphadenopathy (40.2%), hypersensitivity to mosquito bites (32.9%), skin rash (25.6%), hydroa vacciniforme (9.8%), diarrhea (6.1%), and uveitis (4.9%). At the time of onset, 42% of the patients had an infectious mononucleosis–like illness. Life-threatening complications included hemophagocytic syndrome (24.4%), malignant lymphoma (18.3%), disseminated intravascular coagulopathy (15.9%), hepatic failure (14.6%), digestive tract ulcer/perforation (11.0%), coronary artery aneurysms (8.5%), central nervous system involvement (8.5%), myocarditis (6.1%), inter-

### RESULTS

#### Epidemiology.

In total, 82 patients with CAEBV (42 male and 40 female patients) were enrolled in this study. The age at the onset of disease ranged from 9 months to 53 years (mean, 11.3 years). Of the 82 patients, 47 were still alive after 8 months to 18 years of observation (mean, 6.4 years). Thirty-five patients (43%) had died, after survival periods that ranged from 5 months to 12 years after onset of CAEBV (mean, 4.3 years). Causes of death included transplantation-related complications (n = 7), malignant lymphoma (n = 6), digestive tract bleeding/perforation (n = 6), hepatic failure (n = 3), hemophagocytic syndrome (n = 3), leukemia (n = 2), multiple organ failure (n = 2), unknown (n = 2), and other (n = 4). Sixteen patients had undergone hematopoietic stem cell transplantation. Eight of the 16 were alive after 4–41 months of remission. One patient relapsed and died shortly afterward. The other 7 patients died of transplantation-related complications, which were defined as complications that occurred within 60 days of transplantation and were considered to be associated with transplantation and not with the disease itself. The transplantation-related complications included sepsis (n = 2), veno-occlusive disease (n = 1), graft-versus-host disease (n = 1), thrombotic microangiopathy (n = 1), pneumonia (n = 1), and pulmonary edema (n = 1). There were no remarkable or common family or medical histories among the patients with CAEBV.
Table 5. Multivariate analysis of factors related with Epstein-Barr virus infection–associated mortality.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver dysfunction</td>
<td>5.2 (0.78–34.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7.9 (1.15–54.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Fever &gt;1 day/week</td>
<td>2.5 (0.52–12.2)</td>
<td>.25</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>5.5 (0.73–42.0)</td>
<td>.07</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.7 (0.38–18.6)</td>
<td>.30</td>
</tr>
<tr>
<td>Age at disease onset</td>
<td>1.08 (1.01–1.15)</td>
<td>.02</td>
</tr>
</tbody>
</table>

NOTE. P values were obtained by use of logistic regression analysis. Statistically significant results are shown in boldface type. CI, confidence interval.

Figure. 1. Probability of survival calculated from Kaplan-Meier estimates. A, All patients (n = 82); probabilities of survival at 5 and 10 years were 0.68 ± 0.06 and 0.58 ± 0.07, respectively. B, Comparison between patients at >8 years from disease onset (n = 45) and patients at <8 years from disease onset (n = 37); probability of survival at 5 years was 0.45 ± 0.09 for older patients and 0.94 ± 0.04 for younger patients (P < .001). C, Comparison between patients with thrombocytopenia (platelet count <12 × 10^4 platelets/μL at diagnosis; n = 59) and those without thrombocytopenia (platelet count ≥12 × 10^4 platelets/μL; n = 20); probability of survival at 5 years was 0.38 ± 0.13 for patients with thrombocytopenia and 0.76 ± 0.06 for those without thrombocytopenia (P = .001). D, Comparison between patients with T cell–type disease (n = 38) and patients with NK cell–type disease (n = 27); probability of survival at 5 years was 0.59 ± 0.09 for those with T cell–type disease and 0.87 ± 0.07 for those with NK cell–type disease (P = .009).

stitial pneumonia (4.8%), and leukemia (4.8%). With the exception of the patients who had undergone transplantation, only 4 patients experience remission 3–9 years after onset. The remaining patients with CAEBV generally had continuous symptoms during the observation periods, although they showed some fluctuations.

EBV-related antibody titers were measured in 81 patients. The positivity rates and titers of the antibodies are shown in table 1. All the patients examined were HIV-antibody negative. Surface marker analysis was performed in 74 patients: 3 patients had high CD4^+ cell counts (defined as >70% of the lymphocytes); 5 patients had high CD8^+ cell counts (defined as >50% of the lymphocytes); and 15 patients had high CD56^+ cell counts (defined as >50% of the lymphocytes). Lymphocyte mitogen responses were measured in 34 patients, 32 (94%) of whom had responses within the normal range. Virus load was measured in 60 patients by means of quantitative PCR or in situ hybridization. The data on virus loads in peripheral blood are summarized in table 2. All the patients examined had high virus loads and fulfilled ≥1 criterion, as described in the case definition. However, virus load values were variable and difficult to compare, because different analytic methods were used with different sample sources. The clonality of EBV was analyzed in 54 patients, of whom 41 (76%) were monoclonal, 7 (13%) were oligoclonal, and 6 (11%) were polyclonal. EBV-infected cells were as follows: T cells (n = 38 patients), NK cells (n = 27), B cells (n = 2), combined T and NK cells (n = 3), unclassified (n = 4), and not done (n = 8). Although some patients exhibited mixed lineages, in general patients could be divided into 2 groups: patients with T cell infection (T cell type; n = 38) and those with NK cell infection (NK cell type; n = 27). The 2 patients with B cell infection had the typical symptoms and progression of CAEBV and fulfilled the
cells were not completely excluded by this method. Although infections of T and NK cells were not completely excluded by this method.

**Mortality risk factors.** The 82 patients were divided into living (n = 47) and deceased (n = 35) patients, and the clinical and laboratory characteristics of these groups were compared. The comparisons of laboratory data at diagnosis are shown in table 3. The deceased patients had lower white blood cell, red blood cell, and platelet counts. The living patients had higher IgE concentrations than did the deceased patients. There were no differences in the titers of serum transaminases, lactate dehydrogenase, and EBV-related antibodies between the 2 groups at the time of diagnosis.

We also evaluated mortality-associated factors by using univariate and multivariate analyses. First, life-threatening complications were investigated. Although almost all the complications were significantly related to increased risk of mortality by univariate analysis, multivariate analysis indicated that digestive tract ulcer/perforation (odds ratio [OR], 11.3; 95% confidence interval [CI], 1.06–120; P = .02) and cardiac complications (coronary artery aneurysms or myocarditis; OR, 7.7; 95% CI, 1.25–47.1; P = .02) were associated with death. However, we considered that these complications were inappropriate as prognostic factors, because they develop late in disease. In fact, digestive tract ulceration/perforation is one of the most frequent causes of death among patients with CAEBV. The pathogenesis of digestive tract ulcer/perforation is unclear and may be heterogeneous. In 1 patient with jejunal ulcer and perforation, pathological findings showed that EBV-infected T cells had infiltrated the lamina propria of the mucosa, which indicates the direct invasion of EBV-infected cells.

Then we evaluated factors that were present at the time of diagnosis or that did not change afterward, which included major signs and symptoms, laboratory data at diagnosis, age at disease onset, EBV-specific antibodies, EBV-infected cells, clonality of EBV, and HLA type. Univariate analysis showed that liver dysfunction, thrombocytopenia, fever, splenomegaly, anemia, and disease onset age correlated significantly with increased risk of mortality (table 4). Patients with infections of the T cells tended to have poorer prognoses. On the other hand, patients who had infection of the NK cells and hypersensitivity to mosquito bites generally had better outcomes. Interestingly, the monoclonality of EBV did not correlate with an increased risk of mortality. The 6 factors that were associated with mortality by univariate analysis were analyzed further by multivariate logistic regression analysis. By using multivariate analysis, we found that only thrombocytopenia and age at disease onset were associated with increased mortality (table 5).

**Survival probability.** The survival probabilities for 82 patients with CAEBV are shown in figure 1A. The survival rates were compared between patients who either had or lacked the risk factors that were identified in the multivariate analysis. In the comparison of ages at disease onset, “8 years” was chosen as the cutoff between the younger and older groups, because the most prominent differences in the 5-year survival rates occurred at this level. Similarly, 12 × 10^9 platelets/μL was chosen as the cutoff for comparisons of platelet counts. Patients with late onset (onset age ≥8 years) had significantly reduced survival times (figure 1B). The probability of 5-year survival was 0.45 ± 0.09 for older patients and 0.94 ± 0.04 for younger patients. Patients with thrombocytopenia (platelet counts <12 × 10^9 platelets/μL) also had significantly lower survival times (figure 1C). We recently reported the results of a small-scale study in which patients with T cell–type CAEBV had lower survival times, compared with those with NK cell–type CAEBV [6]. To confirm this result, the survival probabilities were compared between patients with T cell–type and NK cell–type CAEBV (figure 1D). Once again, the survival of patients with T cell–type CAEBV was significantly lower, compared with that of patients with NK cell–type CAEBV.

**DISCUSSION**

This is the second national survey of CAEBV to have been conducted in Japan. The first survey, which was performed in 1989 and reported by Ishihara et al. [20], consisted only of cases of CAEBV that occurred in children. That survey described the clinical and laboratory features of CAEBV and showed that the disease had high mortality and high morbidity with life-threatening complications. The present (second) survey comprised cases of CAEBV infection that had been diagnosed after 1990 and included cases of CAEBV in both children and adults. The clinical features of CAEBV have changed in the decade that has elapsed between these 2 surveys, which is probably a result of an increase in the sensitivity of detection. Indeed, the prevalence of major signs and symptoms in this survey differs somewhat from the first survey. Recently, cases of CAEBV have been reported that lacked major organ involvement and in which only skin symptoms, such as hypersensitivity to mosquito bites or hydroa vacciniforme-like eruptions, were seen [21–23]. It seems that recent developments in detecting viral genomes and quantifying virus load have extended our understanding of the disease.

The pathogenesis of CAEBV is unclear. However, there is accumulating evidence that clonal expansion of EBV-infected T or NK cells may be associated with the development of CAEBV [8, 9, 19, 24–26]. We recently showed that the majority of patients with CAEBV had either the T or the NK cell type and that these 2 types have different clinical and laboratory features [6]. T cell–type disease was characterized by fever and...
high titers of EBV-related antibodies, whereas hypersensitivity to mosquito bites and high concentrations of IgE were observed in patients with NK cell–type disease [6]. High concentrations of IgE and high prevalence of hypersensitivity to mosquito bites were seen in the living patients in this study, which apparently reflects the more favorable prognosis of NK cell–type patients.

It remains unclear whether these 2 manifestations of disease represent different entities or simply appear to be different due to the nature of the infected cells [6]. Nevertheless, the expansion of EBV-infected T or NK cells may be crucial to the pathogenesis of CAEBV [12], because the vast majority of patients with CAEBV belong to either the T or NK cell–type category. Interestingly, many papers concerning CAEBV have originated in Japan. The genetic backgrounds of Japanese people may be associated with the functions of virus-specific or nonspecific lymphocytes that allow for the expansion of EBV-infected T or NK cells. It is noteworthy that EBV-associated hemophagocytic syndrome, in which EBV infection of T cells plays a pivotal role [27–29], has been reported frequently in East Asia [1]. On the other hand, CAEBV in the Western hemisphere may not always be associated with the expansion of EBV-infected T or NK cells. CAEBV in the Western hemisphere is usually milder than CAEBV in Japan [30]. CAEBV in Japan may be a different entity from CAEBV in the West; if so, it would be better to call the Japanese disease “severe chronic active EBV infection” [10] or “EBV-associated T/NK cell lymphoproliferative disease” [12].

The types of treatment given could have some effect on the outcome of CAEBV disease. However, numerous treatments were administered to each patient in the present study; these regimens were not standardized, because this study was carried out at multiple centers and in a retrospective manner. Therefore, we could not analyze the types of treatment used on the patients in this study. For CAEBV patient mortality, we identified several risk factors that were determined at the time of diagnosis or that did not change afterward. This information is particularly important in selecting specific treatments. Hematopoietic stem cell transplantation, which is reported to be effective in treating CAEBV, constitutes a substantial risk to the patient. Indeed, 7 of the 16 patients who had undergone transplantation died of transplantation-related complications. Patients with CAEBV may have a higher risk of transplantation-related complications, because they often suffer from multiple organ failure and life-threatening complications [6, 20]. As for transplantation-related complications, veno-occlusive disease is of great concern, because most patients with CAEBV have chronic hepatitis, as shown in this study. Nevertheless, patients with poor prognoses require aggressive therapies to reduce or eliminate EBV-infected T or NK cells. Hematopoietic stem cell transplantation has become substantially safer in recent years. Furthermore, the outcome of transplantation might improve if the procedure was implemented before the condition of the patient deteriorated. From our data, we propose that aggressive treatments, such as hematopoietic stem cell transplantation, should be considered for patients who have the following: age at disease onset ≥8 years, T cell infection, or thrombocytopenia (platelet count <12 × 10⁶ platelets/μL). Furthermore, digestive tract ulcer/perforation and cardiac complications are mortality risk factors, although by the time these complications become apparent, it might be too late to formulate treatment strategies.

To confirm the efficacy of transplantation and to establish safer conditioning regimens, prospective studies are needed in which larger populations of patients with CAEBV are assessed.

Acknowledgments

We thank Stephen E. Straus (National Institutes of Health) for a critical reading of the manuscript. We are grateful to all the clinicians who kindly provided clinical and laboratory data for the patients.

References


