

Treatment of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis: Study protocol of a prospective pilot study

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Abstract

In this manuscript, a number of debatable issues related to the diagnosis and treatment of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis (EBV-HLH) will be addressed. Considering the heterogeneous nature of EBV-HLH, diagnostic efforts are required to

clarify the precise nature of the disease at diagnosis, the number of EBV genome copies in peripheral blood, and localization of the EBV genome in lymphoid cells (B, T, or natural killer cells). Although the majority of cases of EBV-HLH develop without evidence of immunodeficiency, some cases have been found to be associated with chronic active EBV infection, genetic diseases such as X-linked lymphoproliferative disease (XLP, type 1, or type 2), or familial HLH (FHL, types 2-5). Due to such background heterogeneity, the therapeutic results of EBV-HLH have also been found to vary. Patients have been found to respond to corticosteroids alone or an etoposide-containing regimen, whereas other patients require hematopoietic stem cell transplantation. Thus, decision-making for optimal treatment of EBV-HLH and its eventual outcome requires evaluation in consideration of the precise nature of the disease. A protocol for a pilot study on the treatment of patients with EBV-HLH is presented here.

Key words: Hemophagocytic lymphohistiocytosis; Epstein-Barr virus; Immune-chemotherapy; Rituximab; Hematopoietic stem cell transplantation

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Core tip: Diagnosis of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis (EBV-HLH) must fulfill both the evidence of EBV infection and the diagnostic criteria for HLH. EBV-HLH is heterogeneous. The majority of EBV-HLH occurs in apparently immunocompetent subjects, but some are associated with chronic active EBV infection status, X-linked lymphoproliferative disease or with familial HLH. Thus, treatment and outcome differ significantly depending on the underlying disease. To find out a most appropriate treatment, various laboratory tests are required to clarify the underlying diseases.

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INTRODUCTION

Epstein-Barr virus-related hemophagocytic lymphohistiocytosis (EBV-HLH) is defined as a hemophagocytic syndrome associated with systemic EBV-related T cell or natural killer (NK) cell lymphoproliferative diseases (LPDs)^[1]. There are two main types of HLH, primary (genetic, inherited) and secondary (acquired)^[2]. EBV-HLH is heterogeneous; the majority of cases of EBV-HLH tend to occur in apparently immunocompetent subjects as secondary disease. However, a number of cases of EBV-HLH have been found to be associated with primary diseases such as familial HLH (FHL)^[3,4] or with X-linked lymphoproliferative disease (XLP, type 1, or type 2)^[5,6]. Recently, various types of primary immunodeficiencies were found to correlate with EBV-proliferative disease^[7]. In EBV-HLH, EBV resides primarily in T cells or NK cells, and is more frequent in Asia and rarely in Western countries^[3,8,9]. The outcome of EBV-HLH has been observed to significantly differ depending on the underlying diseases. Patients with secondary EBV-HLH have been found to respond well to immunotherapy or to chemoimmunotherapy, while patients with EBV-HLH associated with primary diseases require hematopoietic stem cell transplantation (HSCT) due to refractoriness to chemoimmunotherapy^[3]. Thus, genetic studies on FHL and XLP^[2,7,10] are essential to identify whether the patient has a primary condition. In addition, a poor outcome of the patients with chronic active EBV infection (CAEBV)-related HLH has been well recognized in Asia, particularly in Japan^[11]. Although CAEBV has occasionally been reported in Western countries^[12,13], the difference between CAEBV in Asia and Western countries remains elusive. It was reported that in Asia, EBV-infected T cell or NK cells have been found to play a major role in CAEBV, while in Western countries CAEBV primarily involves EBV-infected B cells^[11,12]. In terms of EBV tropism in EBV-HLH, Kasahara and colleagues have demonstrated CD8⁺ T cells to play a major role in acute onset EBV-HLH following initial EBV infection, whereas in CAEBV-HLH, involvement of CD4⁺ T cells or NK cells were primarily found^[14]. The findings that the outcome of CAEBV-related HLH is poor, but the genetic abnormalities of CAEBV have not been identified^[3,14,15] suggest the importance of the identification of major cell types in patients with EBV-HLH upon diagnosis. In addition, in some patients with CAEBV-related HLH that have chromosome abnormalities of EBV-infected cells, a very poor outcome has been reported^[16]. Thus, determination of karyotypes in the peripheral blood,

bone marrow, or biopsied tissue for the prediction of the outcome of patients with EBV-HLH is also desirable. Lastly, viremia is quantitatively identified by determining the EBV genome copy numbers in peripheral blood. Genome copies are obtained per ml of serum/plasma, or per 10⁶ cells (or µg DNA); however, the former is more commonly employed. Responsiveness or refractoriness of EBV-HLH against treatment can be evaluated by determining viral genome copy numbers^[17,18]. Treatment of EBV-HLH has been found to be effective based on the HLH-94 and HLH-2004 type protocols^[19,20] and has been confirmed on a global scale^[21,22]. However, this type of treatment is not required for all cases of EBV-HLH^[23,24]. In acute EBV-HLH, approximately 40% of patients may respond to prednisolone, cyclosporine, or intravenous immunoglobulin (IVIG) treatment, while 60% of patients require an etoposide-containing regimen^[24]. However, details of the results of etoposide therapy, such as the exact duration of treatment or the total dose of etoposide administered to the patients, are unknown. As the HLH-94 and HLH-2004 protocols were originally proposed for primary (familial) HLH^[19,20], the most appropriate treatment for patients with secondary EBV-HLH remains unknown.

DIAGNOSIS OF EBV-HLH

For diagnosis, the diagnostic criteria for HLH^[20] must be fulfilled. Furthermore, EBV involvement must be verified by a positive anti-VCA-IgM (primary infection or reactivation), viremia (> 10³ genome copies/mL of serum or plasma), or a positive EBER-ISH of the bone marrow clot or biopsied tissue section^[3].

UNDERLYING DISEASES ASSOCIATED WITH EBV-HLH

EBV-HLH is a heterogeneous disease and occurs as an acute onset disease upon initial exposure to EBV, or in association with CAEBV, peripheral T cell lymphoma and NK cell leukemia or lymphoma, or a genetic disorder. Genetic disorders associated with EBV-HLH have been identified in patients with XLP (type 1 or type 2), FHL (types 2-5), or other rare genetic diseases^[2,4-7,19] (Figure 1). Diagnostic criteria for CAEBV have been previously proposed^[25]. Acute onset EBV-HLH has been defined as the development of HLH following initial exposure to EBV, while CAEBV-related HLH has been defined as the development of HLH during CAEBV (Figure 2).

TREATMENT RESPONSE CRITERIA IN EBV-HLH

Response to treatment has been defined as follows: initial good response (GR) has been defined as a complete resolution of fever and reduced serum ferritin values (< 500 ng/mL); complete response (CR) has

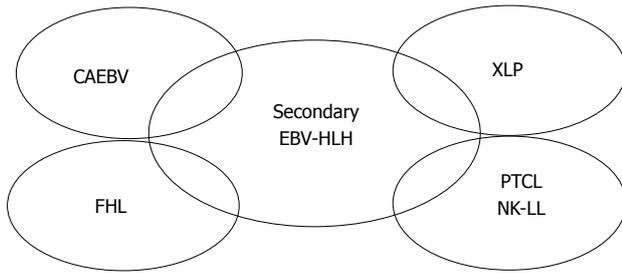


Figure 1 Underlying or other diseases overlapping with Epstein-Barr virus-related hemophagocytic lymphohistiocytosis. Although the majority of cases of EBV-HLH due to secondary HLH develop without any apparent immunodeficiency, some cases may develop in association with CAEBV (see also Figure 2), XLP (type 1 or type 2), FHL (types 2-5), or EBV-positive peripheral T cell lymphoma, or NK cell leukemia or lymphoma. EBV-HLH: Epstein-Barr virus-related hemophagocytic lymphohistiocytosis; CAEBV: Chronic active EBV infection; XLP: X-linked lymphoproliferative disease; FHL: Familial HLH; NK: Natural killer.

been defined as a complete resolution of fever, serum ferritin levels, and EBV genome copies in peripheral blood; and poor response (PR) has been defined as having no reduction of fever and continued high serum ferritin levels (> 500 ng/mL). Relapse has been defined as the recurrence of fever associated with both increased serum ferritin levels and EBV genome copies in peripheral blood. Refractory disease has been defined as the presence of active disease following completion of treatment^[26].

PROPOSED PILOT PROTOCOL

Diagnosis of EBV-HLH is achieved by performing flow cytometry of peripheral blood, quantification of EBV genome copy numbers, and serological detection of anti-EBV-VCA-IgM. The proposed pilot protocol is depicted in Figure 3. Treatment consists of a window period of 2 wk treated with prednisolone (PSL, A1; 2 mg/kg per day). If a GR is attained, PSL with tapering (A2) is further given. At the end of 3 wk of A2 arm treatment, no more treatment is given for patients who attained a CR. Patients with a PR/NR to A1 arm go to B regimen, which consists of weekly etoposide (100 mg/m²), PSL (2 mg/kg) and cyclosporine A (CSA; trough levels 80-150)^[27]. If EBV resides in B cells, 3 doses of rituximab (375 mg/m² per dose) could be added in B regimen^[28-30]. Patients not attaining a CR at the end of B arm treatment go further to C regimen, which consists of once every 2 wk of etoposide (100 mg/m²), PSL (2 mg/kg) and cyclosporine A (CSA; trough levels 80-150). If the patient attains a CR at the end of 24 wk from onset of treatment becomes off treatment and a total cumulative dose of etoposide will be 2200 mg/m². Patients remain at NR/PR at the end of 24 wk of treatment go to a salvage therapy or to HSCT. During the initial 8 wk of treatment, EBV-HLH should be characterized as either acute onset EBV-HLH, CAEBV-related HLH, XLP-related HLH, or FHL-related HLH. Patients demonstrating progressive disease in association with XLP, FHL, or CAEBV should

Correlation of HLH and CAEBV

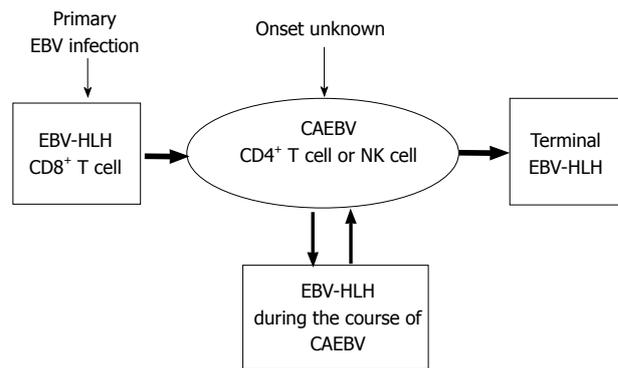


Figure 2 Correlations between hemophagocytic lymphohistiocytosis and chronic active Epstein-Barr virus infection status. CAEBV status may occur without apparent onset of symptoms or may develop following initial acute onset EBV-HLH. During the course of CAEBV, HLH episodes may develop, and if it is not adequately treated by transplantation, most patients eventually succumb to terminal HLH or to lymphoid malignancies. CD8+ T cells play a major role in initial acute onset HLH, whereas CD4+ T cells or NK cells play a role in the status of CAEBV and in CAEBV-related HLH. CAEBV: Chronic active EBV infection; EBV-HLH: Epstein-Barr virus-related hemophagocytic lymphohistiocytosis; NK: Natural killer.

be considered for HSCT as early as possible. Ideally, quantification of the EBV genome copy number should be performed at the onset of treatment, following 4, 8, 24, 28, 72, and 96 wk of treatment, and up to 2 years post-treatment, as indicated in the protocol.

Primary aims of the pilot study

The pilot study treatment protocol will explore the following questions concerning EBV-HLH: (1) what are the major cell types at the onset of EBV-HLH: B cells, CD4+ T cells, CD8+ T cells, or NK cells; (2) how is the CAEBV status initiated? A hypothesis has been previously proposed^[26]. The majority of cases of CAEBV have been suggested to occur insidiously without apparent onset of symptoms, but some cases may develop following initial acute onset EBV-HLH (Figure 2); (3) how high is the incidence (%) of CAEBV-related or genetic disease-related HLH among refractory cases of EBV-HLH; (4) how high is the incidence (%) of patients treated with PSL alone among the CR group? How many patients (%) require treatment using the HLH-94 or HLH-2004 type regimen? What is the correlation between disease type (B cell vs T or NK cell, acute onset vs others) and treatment response; (5) how do changes in EBV genome copy numbers correlate with treatment response; (6) how do changes in serum ferritin levels correlate with clinical symptoms and EBV genome copy numbers; (7) how many doses of etoposide when necessary are required to attain a CR? When can treatment be discontinued in patients with secondary EBV-HLH; (8) how many cumulative doses of etoposide can be safely administered without causing therapy-related acute myeloid leukemia (t-AML); and (9) how does EBV-HLH differ between Asian and Western countries?

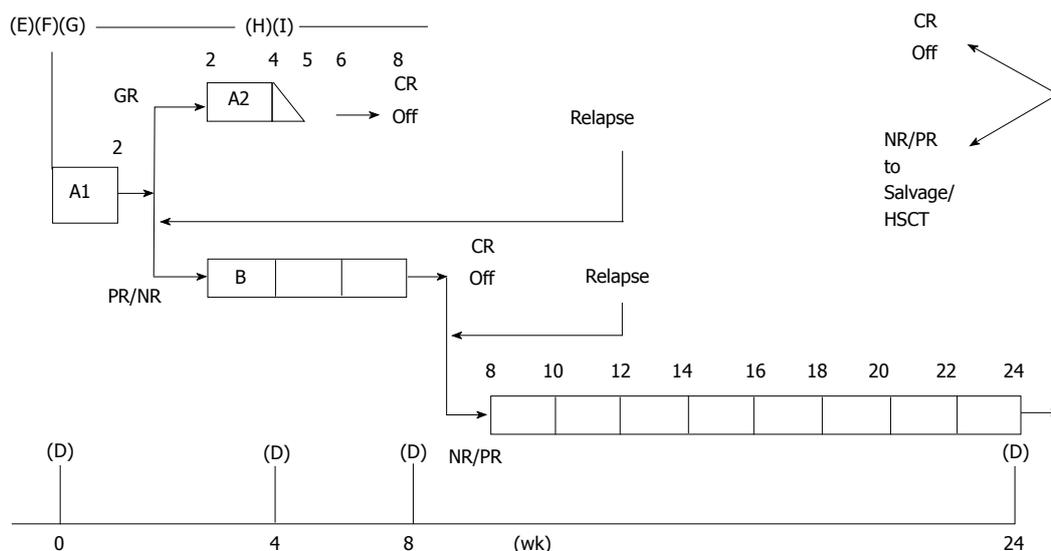


Figure 3 Treatment regimens for Epstein-Barr virus-related hemophagocytic lymphohistiocytosis. Prior to commencement of treatment, determination of EBV genome copy numbers (D), EBV serology (anti-VCA-IgM, -IgG, -EADR-IgG and anti-EBNA) (E), flow cytometry (F), and, if possible, EBV tropism in subsets (G) of PB are required. Furthermore, cytogenetics (H) of PB or bone marrow cells are recommended. It is also recommended to determine EBV genome copy numbers (D) following 4, 8, and 24 wk of treatment to observe treatment response, and following 24 wk, 12, 18, and 24 mo of treatment to determine whether the disease progresses to the status of CAEBV. Screening tests for XLP or FHL are ideally required (I) for any cases demonstrating a PR/NR to the A1 and B regimens until 8 wk of treatment. Treatment comprises a window period of 2 wk commencing with PSL (A1; 2 mg/kg per day). Once a GR is attained, PSL with tapering (A2) is administered. Following 5 wk of PSL given, treatment is discontinued in patients who attain a CR. Patients with a PR/NR to A1 and those relapsed with A2 are to commence the B regimen, which comprises a weekly dose of etoposide (100 mg/m²), PSL (2 mg/kg), and CSA (trough levels, 80-150). If EBV is found to reside in B cells, three doses of rituximab (375 mg/m² per dose) are then added to the B regimen. Patients that do attain a CR becomes off therapy at the end of 8 wk, while who do not attain a CR with B arm treatment are to commence the C regimen, which comprises a once every 2 wk dose of etoposide (100 mg/m²), PSL (2 mg/kg), and CSA (trough levels, 80-150). Patients who relapse after CR with B arm also go to C regimen. If the patient attains a CR following 24 wk of treatment, the total cumulative dose of etoposide is 2200 mg/m². Patients that remain at PR/NR following a total 24 wk of treatment are to undergo salvage therapy or HSCT. GR: Good response; PR: Poor response; NR: No response; CR: Complete response; HSCT: Hematopoietic stem cell transplantation; PSL: Prednisolone; CSA: Cyclosporin A.

DISCUSSION

EBV-LPDs and EBV-HLH

EBV-HLH is a hemophagocytic syndrome occurring in patients with EBV-associated LPDs. The development of EBV-LPD is linked to various hereditary or acquired immune deficiencies^[7], such as XLP1, XLP2, interleukin-2-inducible T cell kinase deficiency, CD27 deficiency, or XMEN (X-linked immunodeficiency with Mg²⁺ defect, EBV infection and neoplasm) syndrome, or may occur post-transplantation. In a study comprising 108 patients with EBV-associated T/NK cell LPDs in Japan, 80 patients were found to have CAEBV, 15 patients were found to have acute onset HLH, nine patients were found to have a severe mosquito bite allergy, and four patients were found to have hydroa vacciniforme^[11]. It remains unclear how HLH occurs in patients with EBV-LPDs. Although EBV-HLH is significantly prevalent in Asia, its incidence and characteristics in Western countries not only require clarification but also a comparison with those observed in Asia.

Heterogeneity of EBV-HLH

Although EBV-HLH may primarily appear to be a secondary disease, it is rather heterogeneous, including high risk diseases such as CAEBV and hereditary diseases. In our previous study comprising 94 EBV-HLH patients, 60 patients were found to be anti-VCA-

IgM-positive, indicating that no primary infectious EBV serological patterns were detected in approximately one third of the patients^[3]. To determine if EBV is found to reside in B cells, CD4⁺ T cells, CD8⁺ T cells, or NK cells, assessment of viral tropism is recommended to be performed at the time of diagnosis, *via* cell sorting and quantification of EBV genome copy counts in each lymphocyte subset. Alternatively, flow cytometry of peripheral blood may be performed to determine the major cell types involved in EBV-HLH (Figure 2).

Quantification of EBV genome copy numbers

The diagnosis of EBV-HLH may be possible using serology alone in cases of a positive anti-VCA-IgM, although determination of the degree of viremia over time is far more useful to assess the response and determine a correlation with the status of CAEBV. Thus, quantifying EBV genome copy numbers in peripheral blood at the onset of HLH and during the course of treatment is highly recommended^[17,18]. Clinically sensitive markers to evaluate EBV-HLH activity include fever, high serum ferritin levels, lactate dehydrogenase, soluble interleukin-2 receptor, and high EBV genome copy numbers. In our previous study, patients with persistently high EBV genome copy numbers in peripheral blood eventually required HSCT due to refractory disease^[18]. However, we recently observed a number of patients who were symptomless and in a

stable condition following discontinuation of treatment for EBV-HLH despite persistent viremia (Unpublished observations). Long-term follow-up may reveal whether these patients relapse as HLH or eventually attain a CAEBV status. There is no consensus on how to best treat these patients.

Acute onset EBV-HLH and CAEBV-related HLH

Previous reports of EBV-HLH potentially comprised a mixture of secondary acute onset HLH, CAEBV-related, or primary/genetic disease-related HLH^[3,31]. In addition to genetic diseases, the CAEBV status should be taken into account in cases of EBV-HLH. Patients with CAEBV are accompanied with dermal symptoms defined as hypersensitivity to mosquito bites or hydroa vacciniforme, and development of HLH in association with clinical features such as infectious mononucleosis-like symptoms, lymphadenopathy, adult onset Still's disease-like symptoms, cardiovascular complications, or cerebellar ataxia or encephalitis^[11,32-34]. In EBV-HLH, classification of secondary HLH as either occurring upon initial exposure to EBV or due to reactivation in association with CAEBV is essential, as the outcome significantly differs between the two^[15,24]. We have previously observed approximately 85% of patients with EBV-HLH to be treated with immunochemotherapy alone compared with 15% who required HSCT^[31]. Patients who underwent HSCT were most likely to comprise high risk groups such as CAEBV-related HLH, XLP-related HLH, or FHL-related HLH.

Treatment of EBV-HLH

In the treatment of EBV-HLH, administration of an etoposide-based regimen within 4 wk of diagnosis has been found to have a beneficial effect^[27], although several studies also have reported a CR in a subset of patients using conventional PSL, CSA, or IVIG alone^[23,24]. The proposed study herein may clarify the true nature of the disease and whether treatment with etoposide is necessary. Furthermore, treatment with etoposide should be commenced immediately following 2 wk of prednisolone therapy in cases where PR/NR is observed.

Cumulative doses of etoposide and t-AML

The use of etoposide may be of concern to physicians due to the patients' risk of developing t-AML. In my survey, twelve documented cases of t-AML in HLH have been reported in the literature. (Unpublished observations) The median occurrence of t-AML following HLH treatment has been found to be 26 mo (range, 6 mo to 6 years). Of these 12 cases, the 11q23 abnormality was found in four cases, FAB-M3 leukemia was observed in two cases, FAB-M5 leukemia was found in two cases, and other types of leukemia were observed in four cases. In seven patients, cumulative doses of etoposide were observed to be greater than 3000 mg/m², and doses less than 1500 mg/m² were found in five cases. Based on these data, to reduce the

incidence of t-AML in HLH treated patients, cumulative doses of etoposide should be preferably limited to less than 3000 mg/m². In the proposed pilot protocol presented here, upon completion of treatment in patients who undergo the arm B regimen within 8 wk, the total etoposide dose comprises 600 mg/m². Even if the patients undergo the arm B and C regimens, the total dose comprises 2200 mg/m², which is considered to be in a safe range.

Rituximab treatment

Rituximab is a pre-emptive B-cell-directed therapy and a candidate for the treatment of EBV-HLH in which EBV resides within B cells^[28-30]. However, in the majority of EBV-HLH cases, EBV resides in T cells or in NK cells. As one of the mechanisms behind why T cells or NK cells that lack a receptor for EBV are infected with the virus, EBV-infected B cells are hypothesized to potentially transfer the virus to T cells or NK cells due to contact between EBV-infected B cells and cytotoxic T cells or NK cells. In consideration of this hypothesis, rituximab may even be effective in the treatment of EBV-HLH involving T cells or NK cells^[35]. Whether rituximab administration is applicable for all cases of EBV-HLH remains to be explored. As a salvage therapy, alemtuzumab^[36] and other regimens may also be used. Novel chemotherapeutic agents for the treatment of CAEBV are currently in progress^[37]. It remains unknown if salvage therapy alone may provide a cure for refractory EBV-HLH.

Adoptive cell therapy

Adoptive immunotherapy has been shown to be effective in the treatment of CAEBV^[38,39]. Similar adoptive cell therapies are expected to be effective in refractory EBV-HLH. Based on fetal-maternal microchimerism tolerance, Wang and colleagues infused high doses of HLA-haploidentical maternal peripheral blood mononuclear cells (> 10⁸/kg per infusion) in five patients with EBV-positive T cell-LPD, with CR observed in three patients^[40].

HSCT

In patients with CAEBV-related or genetic disease-related HLH, allogeneic HSCT is essential, although one of the biggest challenges is the timing of the transplant. The overall estimated 3-year survival outcome after HSCT has been found to be 62% (± 12%) in patients with FHL^[19]. In 2008, Sato and co-workers surveyed 74 cases of HSCT in EBV-associated T cell or NK cell-LPDs in Japan that comprised 42 cases of CAEBV, ten cases of EBV-HLH, and 22 cases of EBV-associated leukemia or lymphoma. In the study, the event-free survival rate was found to be 0.561 ± 0.086 for CAEBV, 0.614 ± 0.186 for EBV-HLH, and 0.309 ± 0.107 for EBV-lymphoma or leukemia^[41]. In 2010, Ohga *et al*^[42] analyzed the outcomes of HSCT on 43 FHL and 14 EBV-HLH patients, in which the 10-year overall survival rates were found to be 65.0% ± 7.9% in FHL and 85.7% ± 9.4% in EBV-

HLH patients. Another retrospective study has been performed on CAEBV patients ($n = 17$) who underwent HSCT with a reduced intensified conditioning regimen (RIC) followed by bone marrow transplantation (RIC-BMT), and in patients ($n = 15$) who underwent RIC followed by unrelated cord blood transplantation (RIC-UCBT). Excellent overall survival rates were obtained with RIC-BMT ($92.9\% \pm 6.9\%$) and RIC-CBT ($93.3\% \pm 6.4\%$) ($P = 0.87$)^[43]. In a more recent study, all five CAEBV patients who underwent HSCT have been reported to be alive without any serious regimen-related toxicity for more than 16 mo following HSCT^[44]. In consideration of these results, HSCT may be safely performed in patients to obtain a cure for refractory EBV-HLH or CAEBV. In addition, the efficacy of UCBT in combination with the RIC regimen has been confirmed in the treatment of EBV-HLH and CAEBV. However, decision-making concerning the determination of the optimal time to perform transplantation at a particular stage of the disease is often difficult in patients that remain in a stable condition, although HSCT may be a curable measure for CAEBV-related HLH and other hereditary disease-related EBV-HLH.

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