Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults and adolescents—a life-threatening disease: analysis of 133 cases from a single center

Wenyuan Lai, Yini Wang, Jingshi Wang, Lin Wu, Zhili Jin and Zhao Wang

Department of Hematology, Beijing Friendship Hospital, Capital Medical University, Beijing, People’s Republic of China

ABSTRACT

Objectives: Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis is the most common type of infection-associated HLH. Previous studies were focused on pediatric EBV-HLH patients, therefore there lack of adult data.

Method: We performed a retrospective analysis of 133 EBV-HLH patients (≥ 14 years old) in Beijing Friendship Hospital from March 2009 to April 2016 to evaluate the clinical manifestation and the effects and prognosis of existing regimens of EBV-HLH in adult and adolescents.

Results: Of these patients, 91 male and 42 female cases had a median age of 26 (14–77) years. EBV-DNA load on admission was at a median of 6.6E + 05 IU/ml. The one-year mortality of these patients was 78%. 112 patients received the HLH-94/04 regimen as the initial treatment, 52 patients (46.43%) had response. Of the 6 patients who received the L-DEP regimen as the initial treatment, 5 patients (83.33%) had response. The rest 15 patients received initial treatment without etoposide, 5 cases achieved PR. 69 refractory or relapsed patients received DEP or L-DEP regimen, 55 (79.71%) cases had response. In addition, who received the L-DEP regimen, with the overall response rate significantly higher than the DEP regimen (88.37% VS 65.38%, P = 0.031). 36 out of 133 EBV-HLH patients eventually received allo-HSCT, with the overall survival rate of 52.78%. In summary, EBV-HLH is a highly lethal disease.

Conclusion: DEP/L-DEP was a good salvage treatment. L-DEP might be a more effective first-line initial regimen than HLH-94/04 regimen for EBV-HLH. Finally, allo-HSCT is an effective radical treatment for EBV-HLH.

KEYWORDS

Hemophagocytic lymphohistiocytosis; Epstein-Barr virus (EBV); adult and adolescents

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an immune disorder characterized by uncontrolled activation of lymphocytes, monocytes, and macrophages, and overgrowth of inflammatory cytokines. The condition manifests as a persistent fever, hepatosplenomegaly, pancytopenia, and hemophagocytosis in bone marrow, liver, spleen, and lymph nodes.

HLH is classified in 2 categories according to the different causes, i.e. familial HLH and acquired HLH. Patients with familial HLH have a dominant inherited disorder or genetic defect. Familial HLH is an autosomal recessive genetic disease with a high incidence in infancy and early childhood. In recent years, a number of studies have shown that familial HLH also occurs in adulthood [1]. Acquired HLH is mostly caused by infection, malignant tumors, and autoimmune diseases and is more common in adults, accounting for approximately 90% of the HLH patients; 32.64% of the adult patients have infection-related HLH, and the most common infection-related HLH is caused by Epstein-Barr virus (EBV), accounting for approximately 70% of infection-related HLH [2].

A previous study showed that EBV does not only directly lead to HLH, but it also acts as a driving factor to promote the disease progression of other types of HLH, which include the most common lymphoma-associated HLH and familial HLH [3].

Although EBV-HLH has aroused more and more attention from researchers in recent years, most of the studies have focused on pediatric patients, but not on adolescents and adults. To improve the understanding of EBV-HLH in adolescents and adults, we conducted a retrospective analysis in EBV-HLH patients to evaluate the clinical manifestations and different curative responses and prognoses of EBV-HLH patients ≥ 14 years old in Beijing Friendship Hospital, Beijing, China from March 2009 to April 2016 to provide the theoretical basis for future diagnosis and treatment of the disease.

Research subjects and methods

Research subjects

HLH patients ≥ 14 years of age with EBV infection who were diagnosed and treated in Beijing Friendship Hospital.
Hospital from March 2009 to April 2016 were recruited for this study.

**EBV-HLH definition**

Meet the internationally accepted guidelines HLH-2004 diagnostic criteria [4] together with high values for EBV-DNA copies in peripheral blood or tissues or number of cells containing EBV-encoded small RNA (EBER) in peripheral blood and tissues. Familial HLH and lymphoma-associated HLH complicated with EBV infection should be excluded.

**Assessment of treatment**

The assessment of treatment was previously described in a research study for pediatric HLH [5]. We modified the treatment based on our experience with adult HLH patients. The following quantifiable symptoms and laboratory markers were used to assess the treatment efficacy of the patients in this study: levels of sCD25; ferritin; triglyceride; hemoglobin; neutrophil counts; platelet counts; and alanine aminotransferase (ALT). Patients who recovered all of the above parameters to normal levels were defined as complete response (CR). A partial response (PR) was defined as at least a 25% improvement in 2 or more quantifiable symptoms and laboratory markers by 2 weeks following treatment as follows: sCD25 response was >1.5-fold decreased; ferritin and triglyceride decreased at least 25%; for patients with an initial neutrophil count of <0.5 × 10⁹/L, an increase by at least 100% to >2.0 × 10⁹/L was considered a response; and for patients with ALT >400 U/L, response was defined as an ALT decrease of at least 50%. In addition, regardless of PR or CR, the body temperature of the patients should revert to normal. Patients who did not achieve CR or PR were defined as no response (NR).

**Refractory/relapse EBV-HLH**

The standard definition of refractory HLH has not yet been defined. According to our experience of clinical treatment as well as the evaluation criteria of other international clinical research centers, this study defined refractory HLH as patients who failed to achieve at least PR after 2 weeks of initial therapy [6]. Relapse HLH was defined as a patient with a recurrent of HLH during the consolidation therapy after the initial therapy had inducted the patient to remission.

**Data processing and statistical analysis**

SPSS 22.0 software (SPSS Inc., Chicago, IL) was used for the statistical analysis in this study. Age, gender, types of primary disease, clinical manifestations, relevant laboratory tests, therapeutic regimens, and survival of the patients were statistically analyzed. Normally distributed data were analyzed using a parametric test. Non-normally distributed data were analyzed using a non-parametric test. Patients’ survival was analyzed using the Kaplan-Meier survival curve. P < 0.05 was considered to be of statistically significant difference.

**Results**

**General patient information**

171 HLH patients had EBV infection. Of those, 133 patients were EBV-HLH; 35 patients were lymphoma-associated HLH; 3 of 68 patients who underwent genetic test were diagnosed with primary HLH including one with homozygous mutation in RAB27A, and one with hemizygous mutation in SH2D1A. Of the 133 EBV-HLH patients, 91 were male and 42 were female (male-to-female ratio of 2.17:1), with the median age of 26 years (ranging from 14 to 77 years old).

**Analysis of clinical manifestations and laboratory findings**

Analysis of clinical manifestations and laboratory findings of the 133 EBV-HLH patients showed that the compliance rates of the diagnostic parameters of HLH were 92% in the elevation of serum ferritin, 93.2% in the reduction of 2 or 3 types of blood cells, 91.2% in fever, and 89.5% in splenomegaly, followed by 87.7% in the elevation of sCD25, and 59% in hypofibrinogenemia. However, the positive rates in the reduction of NK cell activity (44.5%) and elevation of triglyceride (34.7%) were less than 50%. Although liver function damage was not included in the diagnostic criteria of HLH, results of our analysis suggested that 80% of the EBV-HLH patients had liver function damage (Figure 1).

The EBV-DNA load in the peripheral blood of the 133 patients ranged from 5.0E + 03 to 7.79E + 09 IU/mL (median of 6.6E + 05 IU/mL). Forty-five EBV-HLH patients were accompanied by disorders in CNS, with an incidence of 33.8%. Since most of the patients with the onset of the disease were accompanied by a coagulation disorder and thrombocytopenia, only 20 patients completed EBV-DNA detection in the cerebrospinal fluid, and 16 of them (80%) had positive results, with the median EBV-DNA load of 6.7E + 03 IU/mL (ranging from 8.2E + 02 to 2.5E + 06 IU/mL). Of the 82 patients who completed the bone marrow flow cytometry, 28 had an abnormal phenotypic
clonal NK or T cells, including 23 patients with abnormal median NK cell ratio of 5.15% (0.76–13.05%) in their bone marrow and 5 patients with an abnormal median T cell ratio of 2.77% (0.18–18.63%) (Table 1).

Treatment

Initial treatment

In 112 patients out of the 133 EBV-HLH patients who received HLH-94/04 regimen (systemic therapy both included etoposide, dexamethasone, and, cyclosporine A), 52 patients (46.43%) achieved effective treatment outcomes, including 22 patients (19.64%) with CR and 30 patients (26.79%) with PR. Of the 6 patients who received the L-DEP (liposomal doxorubicin together with etoposide and highdose methylprednisolone in combination with PEG-asparagase) regimen, 5 patients (83.33%) achieved effective treatment outcomes (including 3 cases of CR and 2 cases of PR), and 1 patient had no response. The remaining 15 out of 133 EBV-HLH patients, who did not receive etoposide-containing regimens in the initial treatment, had 5 cases who achieved partial remission (33.33%) and 10 cases with no response. The above results showed that L-DEP, as the initial treatment, was more effective than the HLH-94/04 regimen; however, given the small number of cases, statistical analysis could not be performed (Figure 2).

Salvage treatment

Sixty-nine refractory or relapsed patients received DEP (liposomal doxorubicin together with etoposide and highdose methylprednisolone) or L-DEP regimen, 55 (79.71%) achieved effective treatment outcomes. Of the 69 patients who received the DEP/L-DEP regimen, there were 26 patients who received DEP, including 17 cases with an effective treatment outcome (5 cases of CR and 12 cases of PR) and 9 cases with no response. In addition, of the 43 out of 69 patients who received the L-DEP regimen, 13 patients (30.23%) achieved CR and 25 patients (58.13%) achieved PR, with the overall response rate significantly higher than the patients who received the DEP regimen (88.37% vs. 65.4%, P = 0.031). Eight patients with refractory or relapse EBV-HLH were treated with rituximab (CD20 mAb), as a salvage treatment, but they all had no response.

Allogeneic hematopoietic stem cell transplantation

In this study, 36 patients eventually received allogenic hematopoietic stem cell transplantation (allo-HSCT), including 30 cases who received allo-HSCT after HLH remission and 6 cases with no remission during allo-HSCT. Of the 36 patients with allo-HSCT, 19 patients (52.78%) survived and 17 patients died (including 6 patients who died of transplant-related death, 8 patients who died of recurrent EBV-HLH, 1 patient who died of transplant-related thrombotic microangiopathy, 1 patient who died of acute graft-versus-host disease, and 1 patient who died of severe pneumonia).

Table 1. Laboratory findings for EBV-HLH diagnosis.

| Laboratory findings | At diagnosis |
|---------------------|-------------|
| WBC, median (range) | 1.94 (0.1–29.7) |
| Hb, median (range) | 88 (39–150) |
| PLT, median (range) | 45 (1–480) |
| ALT, median (range) | 115.5 (14–1129) |
| AST, median (range) | 127 (3.2–2418) |
| T-BIL, median (range) | 26.4 (4.21–334.8) |
| TG, median (range) | 2.03 (0.39–13.3) |
| Ferritin, median (range) | 7441 (88.3–122360) |
| Fibrinogen, median (range) | 1.37 (0.2–5.49) |
| NK cell activity, median (range) | 15.61 (1.22–67.1) |
| sCD25, median (range) | 26383.9 (802–44000) |
| EBV-DNA, median (range) | 660000 (5000–7790000000) |

WBC: White Blood Cell; Hb: Hemoglobin; PLT: Platelet; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; T-BIL: Total bilirubin; TG: Triacylglyceride; sCD25: soluble IL-2 receptor.
Through the prognostic analysis in the patients before allo-HSCT (according to their HLH conditions), survival of the patients undergone allo-HSCT after HLH remission was significantly higher than who received allo-HSCT without remission (56.67% vs. 33.33%, $P < 0.001$). Of the 97 patients who did not receive allo-HSCT, 85 of them died, and 2 survived, 10 lost to follow up, with the overall survival rate of 0.66%.

**Survival and prognosis**

Of the 133 patients with whom we followed up until July 2017, 21 patients survived, 10 lost to fellow up, and 102 died, with the overall mortality rate of 82.1%, one-year mortality of 78%, and median survival of 3.5 months (ranging from 0.3 to 60.9 months). Multivariate logistic regression was used to analyze the impact of age, gender, reception of allo-HSCT or not, EBV copy number, presence or absence of CNS disorders, chronic active EBV infection or not, and remission after the initial treatment on the patients’ survival. The results showed that remission after the initial treatment and implementation of HSCT had significant impacts on the survival and prognosis of the EBV-HLH patients. Patients with at least PR after the initial treatment had a significantly better prognosis than the patients with no remission after the initial treatment ($P = 0.016$). In addition, patients who received HSCT had a significantly better survival rate than patients who did not receive HSCT ($P < 0.001$) (Figure 3). In this study, we evaluated the prognosis of the patients who achieved CR after the initial treatment and performed survival analysis of the patients who achieved PR after the initial treatment. The results showed that the survival of the patients who achieved CR was significantly better than the patients who achieved PR after the initial treatment ($P = 0.024$).

**Discussion**

HLH is a systemic inflammatory response syndrome caused by defects in familial or acquired immune
regulation, with acute and vigorous onset and high mortality. According to the diagnostic criteria of the Histiocyte Society that were issued in 2004, HLH is divided into familial and acquired forms, and 90% of the adult patients suffer from acquired HLH [4]. Infection plays an important role in acquired HLH, especially EBV infection. Acquired HLH caused by the EBV infection accounts for approximately 70% of infection-associated HLH [2], with significantly higher incidence in the Asian population than in European and North American population, indicating that there is a genetic background of EBV infection. In EBV-HLH, EBV mainly infects CD8 + T cells [7], which express EBV latent membrane protein (LMP-1) after being infected and causes a massive release of cytokines through tumor necrosis factor receptor associated factor (TRAF) to activate the NF-κB pathway to promote T lymphocyte proliferation [8].

EBV infection can be found in EBV-HLH, familial HLH, and lymphoma-associated HLH patients. Familial HLH is divided into non-EBV-induced familial HLH, EBV-induced familial HLH, and immune deficiency syndrome-associated HLH. The latter 2 forms of familial HLH are associated with EBV infection. The presence of an EBV infection is differentiated from 4 types of familial HLH (familial HLH type 2 (FHL2) with PRF1 mutation, familial HLH type 3 (FHL3) with Munc 13-4 or Unc13D mutation, familial HLH type 4 (FHL4) with syntxin-11 mutation, and familial HLH type 5 (FHL5) with Munc 18-2 or STXBP2 mutation [9,10]. In addition, Marsh et al. [11] reports that patients with a 60% SAP gene defect and a 30% XIAP gene defect may develop EBV-HLH. Therefore, EBV-HLH relapses especially in young children and adolescents, and screening to exclude familial HLH is necessary. In adult patients, EBV infection is often associated with lymphoma and is most commonly found in NK/T cell lymphoma. Since lymphoma-associated HLH accompanied by EBV infection is difficult to distinguish from EBV-HLH, pathological biopsies obtained from multiple sites or PET/CT are necessary to exclude the lymphoma cases. In our center, more than one-fourth of the HLH patients with EBV infection were categorized as lymphoma-associated HLH, and NK/T cell lymphoma was the most common. A very small number of HLH patients with EBV infection was familial HLH; thus, familial HLH and lymphoma-associated HLH cases should be excluded from the HLH patients with EBV infection before the diagnosis of EBV-HLH.

The diagnosis of HLH is currently based on the diagnostic criteria of HLH-2004. In this study, the probabilities of fever, elevated ferritin, reduction of 2 or more types of cells in the blood, splenomegaly, elevated sCD25, and hemophagocytosis in EBV-HLH patients were over 85% while the incidences of elevation of fibrinogen and triglyceride and reduction of NK cell activity were below 60%. Reduction of NK cell activity was common in familial HLH cases; however, acquired HLH cases also showed decreased or missing activity of NK cells, which was restored to normal levels after efficient treatment and remission of the disease [12,13]. EBV-HLH is an acquired HLH, which is different from the patients with familial HLH, with the probability of NK cell dysfunction being significantly lower than familial HLH. In addition, EBV-HLH patients in our hospital received non-initial treatment, with a certain recovery from NK cell dysfunction after treatment in a previous hospital, resulting in the high normal rate of NK cell activity of the HLH patients in this study. One study [14] showed enhancement of proliferation of latent EBV-infected lymphocytes and that they contained new surface epitopes. In this study, we found that 34.1% of the EBV-HLH patients had abnormal phenotypes of mature NK/T cells or T-lymphocytes in the bone marrow; however, the bone marrow pathology was not in line with the diagnostic criteria of lymphoma. Given the surface epitopes changes of lymphocytes after the EBV infection of NK/T or T cells, the abnormal mature lymphocytes in the bone marrow of the EBV-HLH patients could not be diagnosed as lymphoma. The diagnostic gold standard of lymphoma in this study was still based on the pathological results.

There is a high mortality rate of EBV-HLH patients without prompt and effective treatment. A previous study showed that the one-year mortality rate of EBV-HLH patients is 75% [15]. The major first-line therapeutic regimens of EBV-HLH included etoposide (VP-16)-based regimens: HLH-94, and HLH-2004 [16]. Etoposide inhibits the core antigen synthesis of EBV, resulting in anti-EBV effects. A previous study in Japan showed that early application of VP-16 reduces the mortality of EBV-HLH in the acute phase, and patients with no VP-16 treatment or delayed VP-16 treatment 4 weeks after diagnosis had a significantly increased risk of death [17]. In our study, the overall response rate of patients who received the initial regimen containing etoposide was higher than the patients who did not receive the etoposide at the initial regimen (48.3% vs. 33.3%). In addition, the survival of the EBV-HLH patients who achieved PR after the initial treatment was better than the EBV-HLH patients with no remission after the initial treatment, suggesting that the early application of VP-16 minimizes the risk of death of EBV-HLH. The Japanese researcher, Imashuku, used VP-16 and dexamethasone-based regimens for EBV-HLH in young children and adolescents, which resulted in 75.6% overall survival (OS) [18]. However, in this study, the remission rate of 112 patients with HLH-94/HLH-2004 was only 46.43%. Since most of the adult EBV-HLH patients in this study were refractory or recurrent cases, the curative response of this type of patient with the HLH-94/HLH-2004 regimen was poor. In addition, the existing large-scale EBV-HLH
studies mainly focused on pediatric EBV-HLH patients, but not on adolescents and adults. There are only a few small-scale studies in adult EBV-HLH patients that showed that the prognosis of adult EBV-HLH patients was significantly poorer than the pediatric EBV-HLH patients [19], which might be one of the reasons for low therapeutic efficacy of HLH-94/HLH-2004 in our EBV-HLH patients. In this study, some patients received L-DEP as the first-line initial treatment and had a better curative response than the patients who received the HLH-94/HLH-2004 regimen, suggesting that L-DEP might be a better first-line treatment for EBV-HLH, which has been validated by our prospective, randomized, and controlled study in our center.

For the patients with refractory EBV-HLH and no remission after the initial HLH-94/HLH-04 regimen and the patients with alleviation after the initial treatment but recurrent EBV-HLH, the available salvage treatments mainly include anti-thymocyte globulin (ATG) [20], tumor necrosis factor alpha (TNF-α) inhibitor [21], anti-CD52 monoclonal antibody [5,22], anti-CD20 monoclonal antibody [23,24], and DEP/L-DEP [25,26]. For the refractory or recurrent EBV-HLH, our previous study shows that the DEP and L-DEP regimens achieved a high treatment efficiency and prolonged the survival time of the patients, and enables more patients to undergo allo-HSCT [25,26]. In this study, our results also showed the very high treatment efficiency of the DEP and L-DEP regimens in the refractory EBV-HLH patients with no remission after HLH-94/HLH-2004 and recurrent patients; and the therapeutic efficacy of L-DEP against EBV-HLH was higher than DEP. In addition, the curative response of anti-CD20 monoclonal antibodies in the patients with refractory/recurrent EBV-HLH in this study was inconsistent with the European reports [23,24]. Given the difference of genetic background of the EBV-HLH patients, EBV mainly infects T lymphocytes in the Asian population but infects both the T and B lymphocytes in Europeans and North Americans; the CD20 monoclonal antibody-targeted inhibition of B cells has no killing effect on the EBV-infected T lymphocytes, and thereby do not effectively scavenging the EBV.

EBV-HLH patients often have multiple immune system abnormalities. A study showed that allo-HSCT reconstructs the immune system of EBV-HLH patients and allows patients to regain the scavenging ability of EBV, thereby prolonging their survival and improving the curative outcomes of the patients [27]. Allo-HSCT may be the only cure for EBV-HLH and may be a prerequisite for refractory and recurrent EBV-HLH patients. Ohga summarized the results of 14 EBV-HLH cases treated with allo-HSCT and showed that 10 patients had an overall survival (OS) of 85.7% [28]. In this study, our results showed that allo-HSCT-treated patients had better survival outcomes than patients who did not receive allo-HSCT. Studies have shown that the OS of EBV-HLH patients without achieving remission before the allo-HSCT is significantly poorer than the patients who achieve remission before the allo-HSCT [29], and allo-HSCT can cause an increase in transplant-related mortality in patients with poorly controlled EBV-HLH. In this study also showed that the survival of patients who achieved CR before or PR after the allogenic HSCT was significantly higher than the patients who did not achieve remission before the allogenic HSCT, and their survival time was also longer.

Conclusion
In conclusion, EBV-HLH is a fatal disease. Our results indicate DEP or L-DEP is an effective salvage therapy. Additionally, L-DEP may be a more effective therapy than HLH-94/2004 regimen to be used as an initial treatment. Finally, allogeneic hematopoietic stem cell transplantation is an effective approach for the treatment of EBV-HLH.

Acknowledgments
ZW contributed to the design of the study. LW, RJP and ZLJ helped with the clinical data collection. YNW and JSW helped with the study design and data analyses. WYL conducted the data analysis and wrote the manuscript.

Disclosure statement
No potential conflict of interest was reported by the authors.

Funding
This work was supported by the Beijing Municipal Science and Technology Plan of Capital Characteristics Project [grant number Z151100004015172], the National Natural Science Foundation of Youth Project [grant number 81401627], and the Capital Health Research and Medical Development Foundation [grant number 2016-2-2027].

References
[1] Wang Y, Wang Z, Zhang J, et al. Genetic features of late onset primary hemophagocytic lymphohistiocytosis in adolescence or adulthood. PLoS One. 2014;9(9): e107386.
[2] Maakaroun NR, Moanna A, Jacob JT, et al. Viral infections associated with haemophagocytic syndrome. Rev Med Virol. 2010;20(2):93–105.
[3] Ishii E, Ohga S, Imashuku S, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol. 2007;86(1):58–65.
[4] Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124–131.
[5] Marsh RA, Allen CE, McClain KL, et al. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with
[6] Jordan MB, Allen CE, Weitzman S, et al. How I treat hemophagocytic lymphohistiocytosis. Blood. 2011;118(15):4041–4052.

[7] Kasahara Y, Yachie A. Cell type specific infection of Epstein-Barr virus (EBV) in EBV-associated hemophagocytic lymphohistiocytosis and chronic active EBV infection. Crit Rev Oncol Hematol. 2002;44(3):283–294.

[8] Chuang HC, Lay JD, Chuang SE, et al. Epstein-Barr virus (EBV) latent membrane protein-1 down-regulates tumor necrosis factor-alpha (TNF-alpha) receptor-1 and confers resistance to TNF-alpha-induced apoptosis in T cells: implication for the progression to T-cell lymphoma in EBV-associated hemophagocytic syndrome. Am J Pathol. 2007;170(5):1607–1617.

[9] Bryceson YT, Rudd E, Zheng C, et al. Defective cytotoxic lymphocyte degranulation in syntaxin-11 deficient familial hemophagocytic lymphohistiocytosis 4 (FHL4) patients. Blood. 2007;110(6):1906–1915.

[10] Cetica V, Pende D, Griffiths GM, et al. Molecular basis of familial hemophagocytic lymphohistiocytosis. Haematologica. 2010;95(4):538–541.

[11] Marsh RA, Madden L, Kitchen BJ, et al. XIAP deficiency: a unique primary immunodeficiency best classified as X-linked familial hemophagocytic lymphohistiocytosis and not a as X-linked lymphoproliferative disease. Blood. 2010;116(7):1079–1082.

[12] Zhang J, Wang YH, Wang JS, et al. The significance of pedigree genetic screening and rapid immunological parameters in the diagnosis of primary hemophagocytic lymphohistiocytosis. Zhonghua Xue Ye Xue Za Zhi. 2016;37(7):565–570.

[13] Ishii E. Hemophagocytic lymphohistiocytosis in children: pathogenesis and treatment. Front Pediatr. 2016;4:47.

[14] Thorley-Lawson DA. Epstein-Barr virus: exploiting the immune system. Nat Rev Immunol. 2001;1(1):75–82.

[15] Zeng X, Wei N, Wang Y, et al. Treatment outcomes and prognostic analysis of 61 Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Zhonghua Xue Ye Xue Za Zhi. 2015;36(6):507–510.

[16] Henter JI, Samuelsson-Horne A, Arico M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunotherapy and bone marrow transplantation. Blood. 2002;100(7):2367–2373.

[17] Imashuku S, Kuriyama K, Teramura T, et al. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Clin Oncol. 2001;19(10):2665–2673.

[18] Imashuku S, Teramura T, Tauchi H, et al. Longitudinal follow-up of patients with Epstein-Barr virus associated hemophagocytic lymphohistiocytosis. Haematologica. 2004;89(2):183–188.

[19] Shiraishi A, Ohga S, Doi T, et al. Treatment choice of immunotherapy or further chemotherapy for Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2012;59(2):265–270.

[20] Mahaoui N, Ouachee-Chardin M, de Saint BG, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. Pediatrics. 2007;120(3):e622–e628.

[21] Hizen T, Nagafuji K, Tsukamoto H, et al. Success with infliximab in treating refractory hemophagocytic lymphohistiocytosis. Am J Hematol. 2006;81(1):59–61.

[22] Strout MP, Seropian S, Berliner N. Alemtuzumab as a bridge to allogeneic SCT in atypical hemophagocytic lymphohistiocytosis. Nat Rev Clin Oncol. 2010;7(7):415–420.

[23] Beutel K, Gross-Wielsch U, Wiesel T, et al. Infection of T lymphocytes in Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in children of non-Asian origin. Pediatr Blood Cancer. 2009;53(2):184–190.

[24] Chellapandian D, Das R, Zelley K, et al. Treatment of Epstein-Barr virus-induced haemophagocytic lymphohistiocytosis with rituximab-containing chemo-immunotherapeutic regimens. Br J Haematol. 2013;162(3):376–382.

[25] Wang Y, Huang W, Hu L, et al. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. Blood. 2015;126(19):2186–2192.

[26] Wang J, Wang Y, Wu L, et al. PEG-asparagene and DEP regimen combination therapy for refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J Hematol Oncol. 2016;9(1):84.

[27] Imashuku S, Hibi S, Ohara T, et al. Effective control of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis with immunochemotherapy. Histiocyte Society. Blood. 1999;93(6):1869–1874.

[28] Ohga S, Kudo K, Ishii E, et al. Hematopoietic stem cell transplantation for familial hemophagocytic lymphohistiocytosis and Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in Japan. Pediatr Blood Cancer. 2010;54(2):299–306.

[29] Kimura H, Ito Y, Kawabe S, et al. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood. 2012;119(3):673–686.