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Short Communication

Lymphoma-based therapy for refractory or relapsed Epstein–Barr virus–related hemophagocytic lymphohistiocytosis in children

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Epstein–Barr virus–related hemophagocytic lymphohistiocytosis (EBV-HLH) is a life-threatening hyperinflammatory syndrome. Although etoposide-based immunochemotherapy has improved survival rates, consensus regarding the appropriate salvage therapy for patients with refractory or relapsed EBV-HLH is lacking. We performed a retrospective study to examine the efficacy of a lymphoma-based treatment regimen for children with refractory or relapsed EBV-HLH. The data of six children were analyzed. Four had cytogenetic abnormalities, and two experienced a transition to EBV-positive T-cell lymphoma. They were treated with an intensive chemotherapy regimen modified from that used in the Berlin–Frankfurt–Münster Group Trial as salvage therapy. Five patients (83%) achieved complete response. Four patients (67%) were disease free for a median of 10 years without undergoing allogeneic hematopoietic stem cell transplantation. No grade 3 or 4 nonhematologic adverse events occurred. Lymphoma-based chemotherapy is a potential curative treatment for some subgroups of children with refractory or relapsed EBV-HLH.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal syndrome of immune system overstimulation characterized by fever, cytopenia, hepatosplenomegaly, and hyperferritinemia. HLH is divided into primary and secondary HLH.[1] Primary HLH is a hereditary immune disorder, whereas secondary HLH is a hypercytokinemia complication triggered by infections, malignancies, and autoimmune diseases. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is required for curing primary HLH. With the introduction of the HLH-94/2004 treatment regimen as a bridge to allo-HSCT treatment, the outcome of primary HLH has improved to a 5-year survival rate of 50%—70%.[2] Epstein—Barr virus (EBV)-HLH is the most common and severe form of secondary HLH and is prevalent among East Asian populations.[3] Activated EBV-infected T cells are responsible for EBV-HLH.[4] EBV infection can stimulate the development of primary HLH in patients with inherited immunodeficiencies and can cause nonneoplastic or neoplastic secondary EBV-HLH.[4,5] Furthermore, patients with severe EBV-HLH have been reported to progress to peripheral T-cell lymphoma (TCL),[6—8] and EBV-HLH and EBV-TCL exhibit many overlapping features.[4,7]

Most patients with EBV-HLH respond to etoposide-based immunochemotherapy. However, 20%—30% of patients with EBV-HLH experience refractory or relapsed (r/r) EBV-HLH and require salvage therapy. Allo-HSCT is recommended for patients with r/r EBV-HLH.[9] However, consensus regarding the appropriate salvage therapy before allo-HSCT is lacking, and few studies have proposed curative therapies for second-line treatment without allo-HSCT. Herein, we present the results of an intensive lymphoma-based treatment regimen as salvage therapy for patients with r/r EBV-HLH.

Patients & methods

We conducted a retrospective review of patient data from January 1998 to December 2015. The patients included in this study were required to (1) meet the diagnostic criteria for HLH[10]; (2) be aged younger than 18 years; (3) have no family history of HLH, underlying immunodeficiency, malignancy, or rheumatologic diseases; (4) have an EBV-associated condition, as confirmed by an immunoglobulin M serological test, EBV viral load, or in situ hybridization of EBV-encoded RNA 1 from a bone marrow (BM) specimen; (5) and have received standard first-line etoposide-based immunochemotherapy. Refractory disease was defined as one exhibiting persistent clinical and laboratory abnormalities after 6 weeks of initial therapy. Relapse was defined as recurrent fever and cytopenia after complete response (CR) for at least 2 weeks.[2,11—14]

All patients were treated according to a protocol (Table S1) based on the Berlin—Frankfurt—Münster Group Trial.[15] The Taiwan Pediatric Oncology Group and an Institutional Review Board approved the study protocol. Clinical and laboratory data were obtained through chart reviews. Central nervous system (CNS) involvement was defined as the presence of any of the following three indicators: neurological signs or symptoms, neuroimaging abnormalities, or pleocytosis determined through cerebrospinal fluid analysis.[16] Survival was defined as the interval between the initiation of salvage therapy and death or the last contact with the patient (or April 30, 2020). Data are presented through descriptive statistics.

Results

Six patients met the inclusion criteria, three men and three women. The median age was 2.7 (1.1—17.1) years. The clinical manifestations are summarized in Table 1. At diagnosis, none of the patients had hypofibrinogenemia, but all six patients' fibrinogen levels decreased to less than 150 mg/dL within 2 weeks. Two patients had CNS involvement at diagnosis. One patient presented with generalized tonic—clonic seizure (patient 4), and another had abnormal signals in the brain magnetic resonance images (patient 6).

One patient was refractory to first-line therapy (patient 1), and five relapsed. Four patients had clonal karyotypic abnormalities, as determined from BM mononuclear cells: three at diagnosis (patients 1, 4, and 5) and one at relapse (patient 6). Two patients experienced the persistence or reappearance of the same karyotypic abnormalities upon treatment nonresponse or relapse (patients 1 and 5), and two received diagnoses of TCL after BM biopsy by pathologists at treatment nonresponse or relapse (patients 1 and 6).

A Swimmer plot of the time course from diagnosis to death or the date of the final follow-up is displayed in Figure 1. The median duration of first-line therapy was 59 (50—86) days. Five patients achieved CR after a median of 41 days. After receiving salvage therapy, five patients achieved CR. The remaining patient exhibited no response to treatment and died (patient 5). Among the five patients achieving CR, the median time to CR was 61 (45—129) days. One patient with peripheral TCL received autologous HSCT. The other four responsive patients completed the salvage chemotherapy, and three experienced sustained CR. One patient experienced a second relapse after developing EBV-TCL and died (patient 6). Four patients survived a median duration of 10 (6—21) years without allo-HSCT. No grade 3 or higher nonhematological adverse events were reported.

Discussion

The results of the retrospective study suggest that a lymphoma-based treatment regimen is potentially curative for children with r/r EBV-HLH. Without allo-HSCT, five patients (83%) achieved CR, and four (67%) were disease free for a median follow-up duration of 10 years. Furthermore, no grade 3 or higher nonhematological adverse events occurred.

EBV-HLH can be mild to severe, and most patients achieved CR after corticosteroid and etoposide chemotherapy. In the HLH-2004 study, 74 patients had EBV at diagnosis, and 68 patients were nonfamilial HLH. Twenty-three patients did not respond to the first-line therapy, and 11 died without undergoing allo-HSCT treatment.[2] The HLH-2004 researchers recommended allo-HSCT for patients with familial, relapsed, or severe or persistent HLH. Notably, six patients with relapsed nonfamilial HLH who restarted the

Table 1 Clinical characteristics of patients with refractory or relapsed Epstein–Barr virus–related hemophagocytic lymphohistiocytosis.

Pt No.	Age/Sex	Clinical and laboratory data at diagnosis											BM EBER1	CNS	Ref or Rel	Outcome/ Month	KA[a]
		Fever	Hepato-spleno-megaly	WBC/ANC (109/L)	Hb (g/dL)	Platelet (109/L)	TG (mg/dL)	Fib mg/dL)	Alb (g/dL)	LDH (IU/L)	Bil (T/D) (mg/dL)	Ferritin (ng/mL)					
1	6Y/M	2 weeks	Yes	1.2/0.16	6.3	67	159	202	3.4	550	0.6/0.1	5838	+	No	Ref	Alive, 262M	Yes
2	3.2Y/F	7 days	Yes	0.6/0.02	9.9	17	284	265	1.9	1768	3.5/3.2	14,004	+	No	Rel	Alive, 77M	No
3	2.2Y/F	4 days	Yes	0.3/0.1	8.5	16	433	405.3	2.8	746	7.3/6.9	9259	+	Yes	Rel	Alive, 128M	No
4	1.6Y/M	3 weeks	Yes	2.6/0.8	9.4	89	382	150.1	3.3	16,822	4.4/4.1	>99,999	+	No	Rel	Alive, 113M	Yes
5	17Y/F	2 days	Yes	1.5/0.9	8.9	49	232	299.8	4.6	742	1.1/0.1	860	+	No	Rel	DOD, 2M	Yes
6	1.1Y/M	10 days	Yes	27/2.7	8.8	77	352	170	2.8	1499	2.8/2.5	5600	+	Yes	Rel	DOD, 7M	Yes

Abbreviations. WBC, white blood cell count; ANC, neutrophil count; Hb, hemoglobin; TG, triglyceride; Fib, fibrinogen; Alb, albumin; LDH, lactate dehydrogenase; Bil (T/D), Bilirubin(total/direct); BM, bone marrow; ERER1, Epstein–Barr virus-encoded RNA 1; CNS, central nervous system involvement; Ref or Rel, refractory or relapsed; DOD, died of disease; KA, Karyotypic abnormalities.

[a] Patient 1 KA: 46, XY, i(18)q(10) at diagnosis and normal karyotype at remission: Patient 4 KA: 46,XY,add(8)(q24) at diagnosis and normal karyotype at remission; Patient 5 KA: 44–47, XX, add(X)(p22.1), ins(3;?)(p21;?),+ins(3;?) (p21;?); Patient 6 KA: normal karyotype at diagnosis and clonal karyotypic abnormalities 46, XY, der(21)t(21;?) at the second relapse.

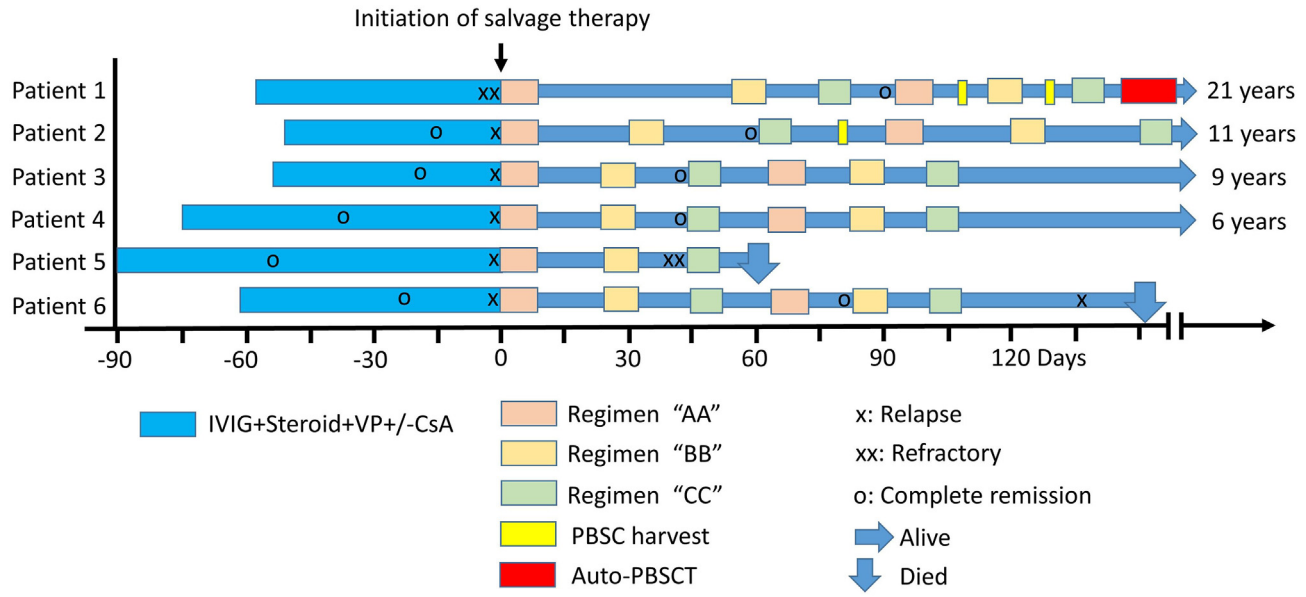

Figure 1 Swimmer Plot of time on treatment for six patients with refractory or relapsed Epstein—Barr virus—related hemophagocytic lymphohistiocytosis. Abbreviations. IVIG, intravenous immunoglobulin; VP, etoposide (VP-16); CsA, cyclosporine; PBSC, peripheral blood stem cells; Auto-PBSCT, autologous peripheral blood stem cell transplantation.

first-line therapy ceased HLH treatment for more than 1 year and survived without receiving allo-HSCT.

Marsh et al. reviewed the literature published from 2000 to 2017 on salvage therapy for refractory primary and secondary HLH.[9] No optimal salvage therapy for bridging to allo-HSCT has been determined. Emapalumab and ruxolitinib have been used to treat r/r HLH[13,17]; however, all responsive patients have eventually relapsed without allo-HSCT. Although allo-HSCT is the standard approach in r/r HLH, the treatment is highly toxic, incurring a 10%—20% risk of treatment-related mortality and a 10%—50% risk of late sequelae.[2,18] Liu et al. reported nivolumab to be a potential cure for r/r EBV-HLH without allo-HSCT,[12] proposing that PD-1 blockade reverses EBV-related and cancer-related immunosuppression and restores immunity to eradicate abnormally activated T cells. This study offers hope for an EBV-HLH treatment alternative to allo-HSCT.[12]

EBV-HLH occurs in children, usually without a genetic etiology. In our study, four patients had clonal karyotypic abnormalities, implicating a clonal entity. Progression to EBV-TCL has been observed among patients with EBV-HLH and karyotypic abnormalities.[6,8] Differentiating severe EBV-HLH from EBV-TCL with current diagnostic modalities is challenging.[4,7] Our four patients with karyotypic abnormalities may have had EBV-TCL; therefore, a lymphoma-based protocol was appropriate. If such a lymphoma-based treatment regimen successfully eradicates abnormally activated T cells, then allo-HSCT may be unnecessary.

Our study has many limitations. No genetic tests were performed to exclude primary HLH, nor were clonal T-cell gene rearrangement studies undertaken to identify neoplastic secondary HLH. Although our patient sample was small, our observations indicate that lymphoma-based chemotherapy may be a viable treatment option for patients with r/r EBV-HLH, especially those with clonal karyotypic abnormalities. Further studies are required to identify subgroups of patients with EBV-HLH who benefit from a lymphoma-based treatment regimen without allo-HSCT.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2022.01.009.

References

1. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood* 2016;**127**:2672—81.
2. Bergsten E, Horne A, Arico M, Astigarraga I, Egeler RM, Filipovich AH, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood* 2017;**130**:2728—38.
3. Chen RL, Lin KH, Lin DT, Su IJ, Huang LM, Lee PI, et al. Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. *Br J Haematol* 1995;**89**:282—90.
4. Coffey AM, Lewis A, Marcogliese AN, Elghetany MT, Punia JN, Chang CC, et al. A clinicopathologic study of the spectrum of systemic forms of EBV-associated T-cell lymphoproliferative disorders of childhood: a single tertiary care pediatric institution experience in North America. *Pediatr Blood Cancer* 2019;**66**:e27798.

5. El-Mallawany NK, Curry CV, Allen CE. Haemophagocytic lymphohistiocytosis and Epstein-Barr virus: a complex relationship with diverse origins, expression and outcomes. *Br J Haematol* 2022;**196**(1):31—44. https://doi.org/10.1111/bjh.17638.
6. Chen JS, Lin KH, Lin DT, Chen RL, Jou ST, Su IJ. Longitudinal observation and outcome of nonfamilial childhood haemophagocytic syndrome receiving etoposide-containing regimens. *Br J Haematol* 1998;**103**:756—62.
7. Smith MC, Cohen DN, Greig B, Yenamandra A, Vnencak-Jones C, Thompson MA, et al. The ambiguous boundary between EBV-related hemophagocytic lymphohistiocytosis and systemic EBV-driven T cell lymphoproliferative disorder. *Int J Clin Exp Pathol* 2014;**7**:5738—49.
8. Chen JS, Tzeng CC, Tsao CJ, Su WC, Chen TY, Jung YC, et al. Clonal karyotype abnormalities in EBV-associated hemophagocytic syndrome. *Haematologica* 1997;**82**:572—6.
9. Marsh RA, Jordan MB, Talano JA, Nichols KE, Kumar A, Naqvi A, et al. *Salvage therapy for refractory hemophagocytic lymphohistiocytosis: a review of the published experience*, vol. 64. Pediatr Blood Cancer; 2017.
10. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;**48**:124—31.
11. Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood* 2011;**118**:4577—84.
12. Liu P, Pan X, Chen C, Niu T, Shuai X, Wang J, et al. Nivolumab treatment of relapsed/refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in adults. *Blood* 2020;**135**:826—33.
13. Wang J, Wang Y, Wu L, Wang X, Jin Z, Gao Z, et al. Ruxolitinib for refractory/relapsed hemophagocytic lymphohistiocytosis. *Haematologica* 2020;**105**:e210—2.
14. Wang Y, Huang W, Hu L, Cen X, Li L, Wang J, et al. Multicenter study of combination DEP regimen as a salvage therapy for adult refractory hemophagocytic lymphohistiocytosis. *Blood* 2015;**126**:2186—92.
15. Seidemann K, Tiemann M, Schrappe M, Yakisan E, Simonitsch I, Janka-Schaub G, et al. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. *Blood* 2001;**97**:3699—706.
16. Horne A, Wickström R, Jordan MB, Yeh EA, Naqvi A, Henter JI, et al. How to treat involvement of the central nervous system in hemophagocytic lymphohistiocytosis? *Curr Treat Options Neurol* 2017;**19**:3.
17. Vallurupalli M, Berliner N. Emapalumab for the treatment of relapsed/refractory hemophagocytic lymphohistiocytosis. *Blood* 2019;**134**:1783—6.
18. Ohga S, Kudo K, Ishii E, Honjo S, Morimoto A, Osugi Y, et al. Hematopoietic stem cell transplantation for familial hemophagocytic lymphohistiocytosis and Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in Japan. *Pediatr Blood Cancer* 2010;**54**:299—306.