Review Article

Narrative review of chronic active EBV infection—advances in clinical management

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Abstract: Chronic active Epstein-Barr virus infection (CAEBV) is a prototype of EBV-associated T- and NK-cell lymphoproliferative diseases (T/NK-cell LPDs). It is a highly progressive disease with fatal organ failure, severe hypercytokinemia ["CAEBV flare"; including hemophagocytic lymphohistiocytosis (HLH)], and overt lymphomatous/leukemic changes. Children and adolescents with CAEBV mostly die within 5–10 years. The progression of adult-onset CAEBV is two-fold faster. We herein present a narrative review. Since CAEBV is a rare disease, limited information is currently available on its treatment. Therefore, we describe our experience of treating CAEBV in addition to a literature review. CAEBV shows a spectrum for its severity and neoplastic nature. Patients will not recover without radical treatment, and mostly require allogeneic hematopoietic stem cell transplantation (HSCT). We established a treatment strategy comprising three steps: cooling [immunochemotherapy with prednisolone (PSL), cyclosporine A (CsA), and etoposide (Etp)], cytoreduction (multidrug-combination block chemotherapy), and reconstruction (allogeneic HSCT). The three-step strategy is applicable to patients at any status of the CAEBV spectrum for improved survival and quality of life. The 3-year overall survival (OS) rate was 76%. Planned HSCT with stable disease or a less active disease status has been successfully performed, and the OS rate is approximately 90%. In contrast, the prognosis of patients with severe disease activity even after chemotherapy is poor (OS rate <20%). Since CAEBV is a progressive disease, the earlier initiation of therapy to complete whole treatment in advance results in better survival. We also discuss new drugs and immunotherapies for CAEBV.

Keywords: Epstein-Barr virus (EBV); chronic active Epstein-Barr virus infection (CAEBV); hemophagocytic lymphohistiocytosis (HLH); hematopoietic stem cell transplantation (HSCT)

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Introduction

Patients with persistent/recurrent illness of Epstein-Barr virus (EBV) infection were initially reported in the 1970s (1,2). These patients were extensively examined, and the concept of chronic active EBV infection (CAEBV) was introduced in the 1980s (3-7). Although EBV was previously shown to exhibit a tropism to a specific subset of lymphocytes, B cells, it was found to infect T and NK cells, resulting in the manifestation of symptoms, in patients with CAEBV in 1988 and 1989, respectively (8-11). B-cell neoplasms and T/NK-cell neoplasms are pathologically considered to differ. Therefore, "CAEBV of the T/NK-cell type" is a new nomenclature (12). CAEBV has historically included B-cell lymphoproliferative disease (LPD) as a small and milder subset in the literature; however, it has been redefined as T- and NK-cell LPD (T/NK-cell LPD) (13,14).

Table 1 Symptoms of CAEBV

Category	Clinical manifestations
IM-like symptoms, major	
Typical	Fever, lymphadenopathy, hepatosplenomegaly, elevated hepatic enzymes (hepatitis), proliferation of granular lymphocytes (in PB)
Other symptoms of CAEBV	
Systemic	Fatigue, headache, myalgia, hypercytokinemia/cytokine storm (tumor lysis syndrome and cytokine release syndrome at treatment)
Blood	Leukopenia, neutropenia, anemia, thrombocytopenia, HLH/HPS
Skin	Typically: small nodule→blister→ulcer→long-lasting scar (following mosquito bites, sunlight/ultraviolet rays, vaccination, or no obvious trigger)
Digestive tract	Gastrointestinal ulcer, bloody stool, melena, oral and pharyngeal aphtha, jaundice, liver failure, pancreatitis
Genitourinary	Genital ulcer, renal dysfunction/failure
Nasal	Nasal congestion, nasal mucosal thickening, sinusitis (without neoplastic bone destruction)
Cardiac	Coronary artery aneurysm/occlusion, myocardial infarction, valvular disease of the heart, arrhythmia, cardiac failure
Large arteries	Cerebral artery aneurysm/occlusion, cerebral infarction/hemorrhage, renal artery aneurysm, renal infarction, splenic artery aneurysm
Respiratory	Respiratory disturbance, pulmonary artery hypertension
Others	Uveitis, neuromuscular manifestations
Differential diagnoses that require attention	Kawasaki disease, Behçet's disease

CAEBV, chronic active Epstein-Barr virus infection; PB, peripheral blood; HLH, hemophagocytic lymphohistiocytosis; HPS, hemophagocytic syndrome.

We herein reviewed advances in the clinical management of CAEBV in our institute and in the literature. This retrospective analysis was approved by the Research Ethics Committee of Osaka Women's and Children's Hospital. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/aol-20-34).

Methods

MEDLINE was searched using the term CAEBV between 1964 and June 2020. Since CAEBV is a rare disease and our department specializes in EBV, we also updated the retrospective analysis of patients with CAEBV treated in our institute before the end of 2019.

Diagnosis

CAEBV

Guidelines for diagnosing CAEBV were proposed in 2005 (15), and comprised the following: (I) persistent or recurrent infectious mononucleosis (IM)-like symptoms, (II) evidence of EBV activation, and (III) the exclusion of other known diseases. The most common symptoms of CAEBV are fever and elevated liver transaminase levels; however, other symptoms have also been reported (*Table 1*) (16). EBV activation is confirmed by abnormally elevated anti-EBV antibodies, with an EBV DNA load ≥317 copies/μg DNA (a rational number is now preferable to an irrational number $10^{2.5}$ for definition) in peripheral blood (PB) mononuclear cells (15). The identification of EBV-infected T/NK cells in PB or affected tissues/organs, together with a medical history and clinical symptoms, is critical for diagnosing CAEBV. EBV-encoded small RNA (EBER) staining with *in situ* hybridization and a flow cytometric analysis was recently developed for rapid identification (17,18). A biopsy of any affected tissues/organs is not mandatory, but is required for a differential diagnosis in some cases (*Table 2*) (12,16,19). CAEBV, a T/NK-cell LPD, is sometimes considered to be similar to a lymphoma, but is a PB-diagnosable lymphoma

Table 2 Classification of EBV-associated T/NK-cell LPD

Clinically defined EBV-associated T/NK-cell lymphoproliferative diseases		Pathologically proposed EBV-positive T/NK-cell lymphoproliferative disorders	
Category	Diagnosis	Diagnosis	Category
Acute/transient	Primary EBV infection-associated HLH, spectrum	EBV-positive HLH (benign lymphoproliferation, may be self-limited)	Acute/transient
		Systemic EBV-positive T-cell lymphoma of childhood	Malignant
	cHV	HV-like LPD (spectrum, classic HV)	Acute/transient
Chronic/progressive	CAEBV, spectrum	CAEBV of T/NK-cell types, systemic form	Chronic/progressive
		Systemic EBV-positive T-cell lymphoma of childhood	Malignant
	CAEBV-related diseases	Cutaneous CAEBV	
	HMB	Severe mosquito bite allergy	Chronic/progressive
	Severe-type/sHV	HV-like LPD (spectrum, severe HV)	
		HV-like LPD (spectrum, HV-like T-cell lymphoma)	Malignant
Malignant	ANKL	ANKL	Malignant
	ENKTL, nasal type	ENKTL, nasal type	
	Hepatosplenic T-cell lymphoma	Hepatosplenic T-cell lymphoma	
	PTCL, NOS	PTCL, NOS	
		Nodal PTCL, EBV-positive (primary EBV-positive nodal T/NK-cell lymphoma)	
Immunodeficiency-associated	PID-associated EBV-associated T/NK-cell LPD	LPDs associated with primary immune disorders (T/NK-cell type)	Immunodeficiency-associated
	Posttransplant EBV-associated T/NK-cell LPD (EBV + T/NK-PTLD)	PTLDs (EBV-positive, T/NK-cell type)	
	Other immunosuppression-associated EBV-associated T/NK-cell LPDs	Other iatrogenic immunodeficiency-associated LPDs (T/NK-cell type)	

Chronic/progressive LPDs are potentially malignant. Any LPD in each patient, which was originally categorized to the acute/transient group, but has lost the proapoptotic nature, is also potentially malignant. EBV, Epstein-Barr virus; LPD, lymphoproliferative disease/disorder; HLH, hemophagocytic lymphohistiocytosis; CAEBV, chronic active EBV infection; HMB, hypersensitivity to mosquito bites; HV, hydroa vacciniforme; cHV, classical HV; sHV, systemic HV; ANKL, aggressive NK-cell leukemia; ENKTL, extranodal NK/T-cell lymphoma; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; PID, primary immunodeficiency; PTLD, posttransplant LPD.

or leukemia.

CAEBV shows a spectrum for its neoplastic nature, and, thus, is regarded as a potentially malignant disease. CAEBV is pathologically categorized as follows: polymorphic polyclonal/oligoclonal LPD, polymorphic monoclonal LPD, and monomorphic monoclonal LPD [similar to posttransplant LPD (PTLD)] (20,21). Based on this definition, truly malignant EBV-associated T/NK-cell LPD, such as aggressive NK-cell leukemia (ANKL) and extranodal NK/T-cell lymphoma (ENKTL), need to be excluded. However, the boundary between CAEBV and malignant T/NK-cell LPD is ambiguous (22-24). Some cases of ANKL and ENKTL developed from CAEBV (25,26). Furthermore, hemophagocytic lymphohistiocytosis (HLH) may emerge during the clinical course as a symptom of CAEBV.

Hypercytokinemia, including hemophagocytic syndrome (HPS) and HLH, is a life-threatening manifestation of CAEBV. Severe hypercytokinemia may rapidly develop, may be fatal in any patient with CAEBV, and is referred to as "CAEBV flare" (16,19). Hypercytokinemia/HLH in CAEBV is generally caused by EBV-infected T/NK cells themselves, indicating that affected cells retain the original nature of cytotoxic cells. Therefore, HLH itself

does not indicate lymphoma/leukemia, including "systemic EBV-positive T-cell lymphoma of childhood". The rapid initiation of treatment is strongly recommended for fulminant cases following the diagnosis of "EBV-associated T/NK-cell LPD (including CAEBV, lymphoma, and leukemia)" without further sub-categorization (13).

Mutations/variants in genes, which may be responsible for primary immunodeficiencies (PIDs), have been incidentally detected in patients with CAEBV (27). PIDs are generally suspected in patients with EBV-associated B-cell LPD. However, similar to PTLD, EBV-associated T/NK-cell LPD may also occur with immune dysregulation (28). CAEBV is diagnosed by the exclusion of other known diseases. Therefore, the relationship between the affected gene variants and the clinical history of patients in view of susceptibility to infections needs to be considered when attempting to reach a diagnosis of CAEBV.

CAEBV-related diseases

Systemic IM-like symptoms follow a topical skin reaction, which is induced by mosquito bites and sunlight in cases of hypersensitivity to mosquito bites (HMB) and severe-type/systemic hydroa vacciniforme (sHV), respectively (*Table 2*). HMB is characterized by a high load of EBV-infected NK cells in the skin and PB, and often has a similarly poor prognosis to CAEBV (29,30). Classical HV (cHV) is a self-limited disease in which EBV-infected gamma delta T cells are harbored in the skin and PB (31). In contrast, sHV has a poor prognosis similar to HMB and CAEBV. sHV is mainly caused by EBV-infected α/β T cells (32-34). EBV may infect two or more subsets of T/NK cells (35,36), and symptoms may manifest based on the nature of the major subset. Although sHV appears to progress from cHV in some cases, it is a distinct disease from cHV rather than a lineage switch in a single affected clone. EBV-infected NK cells have been detected in patients concomitantly manifesting HMB and sHV.

The diagnoses of HMB, sHV, and CAEBV are not mutually exclusive in a single patient with EBV-associated T/NK-cell LPD; therefore, these three are different aspects of one disease, rather than three overlapping diseases. Systemic IM-like symptoms may also be elicited by subcutaneous vaccination in patients with CAEBV. Treatment strategies have primarily been developed in the CAEBV approach, but may also be applied to HMB and SHV. Therefore, the following analyses include patients with CAEBV, HMB, and sHV.

Etiology and prognosis

Patients with CAEBV will not recover without radical treatment. A nationwide questionnaire survey, which was performed in the 1990s in Japan, revealed that 50% of patients with CAEBV died within 5 years, with the majority ultimately dying within 10–15 years (25). The outcome of adult-onset CAEBV is worse, with most patients dying within 5 years (37,38). CAEBV is a severe progressive disease with fatal organ failure (particularly hepatic and cardiac), hypercytokinemia/HLH (resulting in multiple organ failure), and true lymphoma/leukemia.

Although EBV is a B-cell tropic virus, it may infect T/NK cells at a low frequency (39,40). However, EBV-infected T/NK cells cannot be maintained and undergo apoptosis *in vitro* and in a healthy internal environment (41). Therefore, regarding carcinogenesis, EBV-infected T/NK cells in patients with CAEBV appear to have acquired mechanisms to evade apoptosis and self-expand (42). Okuno *et al*. reported an intragenic deletion in the EBV genome in BamH1 A rightward transcript (BART) microRNA clusters 1 and 2 in 35% (27/77) of patients with CAEBV, which promoted lymphomagenesis (36). Somatic mutations were also detected in a number of genes, such as DDX3X, BCOR/BCORL1, and TET2, in 20% (16/80) of patients with CAEBV (36). Some of these somatic mutations were frequently observed in healthy older individuals as clonal hematopoiesis of indeterminate potential (43), which may lead to myelodysplastic syndromes (MDS). Common somatic mutations may provide insights into the initiation and progression of CAEBV, as well as the poor prognosis of adult-onset CAEBV.

Treatment overview

Development of the three-step strategy

Immunotherapy and chemotherapy were attempted in the 1980s and 1990s to treat CAEBV and exerted some clinical effects, but failed to improve the final outcome (44). Regarding the use of anti-cancer drugs against CAEBV, some experts disagreed with its use claiming that CAEBV is just an infectious disease; however, based on our findings that CAEBV is a malignant (potentially neoplastic) disease (10,11), we introduced anti-cancer drugs as a treatment for CAEBV. A male pediatric patient with CAEBV was the first to successfully undergo bone marrow transplantation (BMT) from his HLA-matched elder brother in 1998 (45). Allogeneic hematopoietic stem cell transplantation (HSCT)

Step 1 Cooling	PSL CsA Etp	0.5–2 mg/kg/d po t.i.d. or b.i.d. (or div) 3 mg/kg/d po bis in die (or civ) 150 mg/m^2 weekly div						(during step 2) 0.2–0.3 mg/kg/d po 2–3 mg/kg/d po 100–150 mg/m^2 (on demand)				
Step 2 Cytoreduction (on PSL and CsA)	Modified CHOP (THP-COP)	CPA 750 mg/m^2 (d1), THP-ADM 25 mg/m^2/d (d1–2), VCR 2 mg/m^2 (max 2 mg/dose) (d1), PSL 50 mg/m^2 (d1–5)										
	Capizzi	CA 3 g/m^2 every 12 hrs (d1p.m.–d3a.m.), L-Asp 10,000 U/m^2 (d3p.m.), PSL 30 mg/m^2 (d1–3)										
	HDCA	CA 1.5 g/m^2 × 2/d (every 12 hrs, d1–6), PSL 30 mg/m^2/d (d1–6)										
	VPL	Etp 150 mg/m^2 (d1), L-Asp 6,000 U/m^2 (d1–7), PSL 30 mg/m^2 (d1–7)										
	ESCAP	Etp 150 mg/m^2 (d1), CA 1.5 g/m^2 × 8 (d1p.m.–d5a.m.), L-Asp 6,000 U/m^2 × 5 d (d5p.m.–d9), mPSL 62.5 mg/m^2 × 2/d (d1p.m.–d5), PSL 30 mg/m^2/d (d5–9)										
Step 3 Reconstruction	LDEC	Etp 30 mg/m^2/d civ and CA 20 mg/m^2/d civ for 9 [7–14] days before RIC (day –16 to –8)										
	RIC			d-8	d-7	d-6	d-5	d-4	d-3	d-2	d-1	d0
		Flu	30 mg/m^2/d × 6 d	○	●	●	●	●	●	●		
		Mel	70 mg/m^2/d × 2–3 d						●	●		
		ATG	1.25 mg/kg/d × 2 d (civ)		●→	●→						
		mPSL	250 mg/m^2 × 2/d × 2 d		●●	●●						
		Etp	100 mg/m^2/d × 2–3 d						●	●		
			HSCT									▼

Figure 1 Three-step strategy for the treatment of CAEBV. In step 1 (immunochemotherapy), the initial dosage of PSL is 1–2 mg/kg/d for children and 0.5–1 mg/kg/d for adults. Etp (VP-16) is omitted for patients without HLH. Thereafter, lower doses of PSL and CsA are generally maintained through step 2 (multidrug-combination block chemotherapy), particularly when the burden of residual disease is high, until step 3 (RIC-HSCT). The open circle indicates optional administration. One precedent dose of Mel 70 mg/m^2/d (210 mg/m^2 in total) is for children and adolescents at CBT after three courses or less of chemotherapy, which is replaced by the systemic irradiation of 3 Gy with gonadal blockade in adults. CAEBV, chronic active Epstein-Barr virus infection; PSL, prednisolone; Etp, etoposide; HLH, hemophagocytic lymphohistiocytosis; CsA, cyclosporine A; RIC, reduced-intensity conditioning; HSCT, hematopoietic stem cell transplantation; Mel, melphalan; CBT, cord blood transplantation; iv, intravenous infusion; civ, continuous iv; div, drip iv; b.i.d., bis in die; t.i.d., ter in die; ATG, anti-thymocyte globulin (Thymoglobulin®, Sanofi, France); CA, cytosine arabinoside; CPA, cyclophosphamide; Flu, fludarabine; L-Asp, L-Asparaginase; LDEC, low-dose Etp and CA; mPSL, methylprednisolone; THP-ADR, pirarubicin; VCR, vincristine.

became widely accepted in the late 2000s.

Since the initial success of HSCT, a treatment strategy consisting of three steps has been established (*Figure 1*) (19,46). The typical time schedule of the current treatment is shown in *Figure 2*. Our three-step strategy may also be applicable not only to children and adolescents, but also to adults with CAEBV (19). The 3-year overall survival (OS) rate was previously reported to be 76% (19). Planned HSCT is now performed for patients with stable disease or a less active disease status, i.e., without uncontrolled flare, and the 3-year OS rate is approximately 90%.

HSCT is currently the only cure for CAEBV patients, and complete donor-type chimerism is essential. We treated 92 patients with CAEBV before the end of 2019. Three out of 85 patients who underwent HSCT died soon after treatment (d1, d3, and d4 after HSCT). Among the remaining 82 patients, the cumulative incidence of mixed chimerism, insufficient autologous hematopoietic recovery (auto recovery), and engraftment failure was 2, 1, and 4, respectively. Although all patients with engraftment failure were successfully engrafted with 2nd HSCT, all three with mixed chimerism or auto recovery showed the early recurrence of disease (including one with no overt symptoms). Once complete donor-type chimerism was achieved, relapse was only observed in 3.8% of patients (3/79): one case of systemic relapse and two of local relapse as "hidden spaces" from immune surveillance, namely, the central nervous system (CNS) and skin (47). The numbers of chemotherapy courses received before HSCT were six, two, and two, respectively, EBV loads in PB at conditioning for HSCT were 500,000, 30,000, and 20,000 copies/mL (whole blood), ages at HSCT were 11, 38, and 16 years old, respectively, and the types of HSCT were BMT, umbilical cord blood transplantation (CBT), and CBT, respectively.

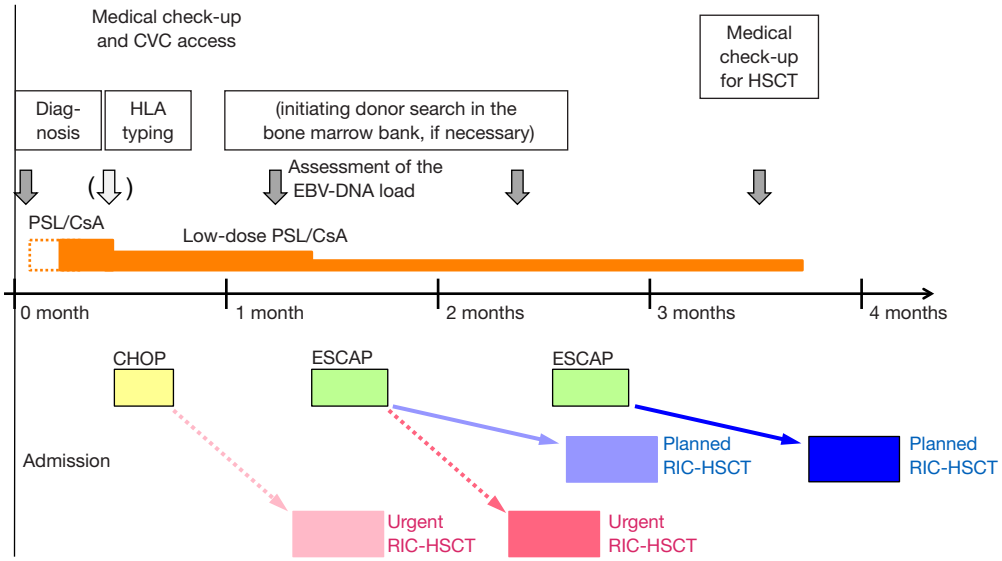

Figure 2 Typical time schedule of the CAEBV treatment. To achieve higher survival rates, the earlier initiation of treatment is considered to complete HSCT in advance. If the EBV-DNA load is <1/10 after recovery from myelosuppression following chemotherapy, it is considered to be effective and is administered again. Urgent RIC-HSCT is considered anytime when a disease is resistant/dependent to chemotherapy. CAEBV, chronic active Epstein-Barr virus infection; HSCT, hematopoietic stem cell transplantation; RIC, reduced-intensity conditioning; CsA, cyclosporine A; CVC, central venous catheter; HLA, human leukocyte antigen; PSL, prednisolone.

As a result, no obvious risk factor for recurrence/relapse was identified other than mixed chimerism/auto recovery as described above.

Optimization of HSCT

In our institute, patients generally undergo HSCT after at least two courses of multidrug-combination chemotherapy. Myeloablative conditioning (MAC) was used in early series. The 1st case of successful reduced-intensity conditioning (RIC) followed by BMT (RIC-BMT) was a patient with well-controlled CAEBV in 2002. RIC was introduced with the aim of reducing late sequelae, and all patients have been treated with RIC since 2006. However, RIC also achieved better survival because of reductions in early toxicity: 3-year OS rates were 91–95% and 55–67% with RIC and MAC, respectively (19,46). The recovery rate of spontaneous menstruation was also higher (82% and 7% with RIC and MAC, respectively) (48). Although azoospermia and precocious menopause need to be considered, female patients and the partners of male patients have successfully become pregnant and given birth.

The 1st CBT for CAEBV to follow RIC was planned and successfully performed in 2003. Since then, we have been improving RIC (49). The latest combination of drugs for RIC was initiated in 2010 and worked well for BMT and peripheral blood stem cell transplantation (PBSCT). However, the rejection rate was higher than expected for CBT (49). We added one dose of melphalan (Mel) 70 mg/m^2 for children and adolescents from 2012 (or systemic irradiation of 3 Gy for adults), which increased the engraftment rate from 57% to 100% (50).

Upfront HSCT without multidrug-combination chemotherapy also represents a treatment option. Although some patients may be cured by this approach, the following issues need to be considered (*Table 3*). (I) The disease activity of CAEBV widely varies. Conditioning before HSCT induces tumor lysis, resulting in conditioning-associated HPS in 33% of patients (49). Although most cases were self-limiting or controlled with etoposide (Etp), fatal conditioning-associated HPS was reported (51). The step-by-step cytoreduction of drug-susceptive EBV-infected T/NK cells is a safer approach. (II) In contrast to benign diseases, complete donor chimerism is required for CAEBV to prevent recurrence. However, even for BMT, RIC is sometimes insufficient, and the acquisition rate of complete

Table 3 Purposes and benefits of chemotherapy prior to HSCT

No.	Expected preferable impacts	Descriptions
1.	To provide a safe bridge to HSCT by reducing EBV-infected cells and suppressing disease activity	Disease flare, which is potentially fatal, may occur at any time
2.	To improve the complete engraftment rate of HSCT, particularly at CBT	Normal T/NK cells are also activated to reject donor cells under the internal environment of hypercytokinemia
3.	To reduce the relapse rate after RIC-HSCT	Chemotherapy may attenuate CAEBV (as an analogy to the management of advanced MDS before RIC-HSCT)
4.	To identify patients who need HSCT, although most patients require HSCT	Patients with the mildest CAEBV may be cured by chemotherapy without HSCT
5.	The stepwise administration of CHOP/THP-COP, ESCAP, and RIC-HSCT is a safer cytotoxic approach for reducing the tumor burden	As an initial treatment, MAC, RIC, and even high-dose chemotherapy may induce fatal flare

HSCT, hematopoietic stem cell transplantation; EBV, Epstein-Barr virus; RIC, reduced-intensity conditioning; CBT, cord blood transplantation; MDS, myelodysplastic syndromes; MAC, myeloablative conditioning.

donor chimerism is not adequate, similar to other diseases [40% in patients with familial HLH (FHL)] (52). (III) Chemotherapy may attenuate CAEBV before RIC-HSCT, similar to the management of advanced MDS before RIC-HSCT (53). (IV) CAEBV is a progressive disease. The earlier initiation of therapy results in better survival. The timing of chemotherapy and HSCT is restricted [case 2 in a previous study (19)] before bypassing "the point of no return" to a fatal clinical course.

Current three-step treatment strategy

Step 1 (cooling): immunochemotherapy

At the diagnosis of CAEBV, immunochemotherapy is initiated as step 1 (cooling) and consists of prednisolone (PSL), cyclosporine A (CsA), and Etp (*Figure 1*). PSL and CsA are used to suppress the abnormal self-activation of EBV-infected T/NK cells and hypercytokinemia, which may induce the activation of macrophages and histiocytes (potential HPS/HLH). A previous study suggested that Etp inhibited EBV nuclear antigen (EBNA) synthesis and EBV DNA synthesis in EBV-infected lymphocytes *in vitro* (54). In addition, high-dose Etp may induce apoptosis in the activated T cells of mice as a model of FHL (55). However, Etp mainly targets activated macrophages, and, thus, may be spared when HLH does not accompany EBV-associated T/NK-cell LPD.

Pulsed high-dose methylprednisolone (mPSL) needs to be considered for progressive hypercytokinemia. If a patient is accompanied by HLH, the HLH-94/HLH2004 protocol may be substituted for step 1, which was originally developed for FHL and consists of dexamethasone (Dex), CsA, and Etp (56,57). However, in contrast to FHL, CAEBV is less likely to involve CNS and Dex has more severe side effects than PSL; therefore, Dex is not mandatory for CAEBV. Further diagnostic examinations, medical check-ups, and other preparations for treatment (including HLA typing) are performed during 2 [1–3] weeks of immunochemotherapy (*Figure 2*). This step achieves the temporary control of disease activity, but does not contribute to the cytoreduction of EBV-infected T/NK cells in CAEBV (*Figure 3*) (58). Patients then move to the next step.

Step 2 (cytoreduction): multidrug-combination block chemotherapy

In step 2, the cytoreduction of EBV-infected T/NK cells is expected. Cytokine release syndrome and HPS/HLH may be induced with the tumor lysis of highly drug-susceptible EBV-infected T/NK cells at the time of chemotherapy and with the homeostatic proliferation of EBV-infected T/NK cells at recovery from myelosuppression (59). Therefore, low-dose PSL and CsA need to be continued during step 2, particularly when the burden of the residual disease is high, and pulsed high-dose mPSL and Etp also need to be loaded for hypercytokinemia and HPS/HLH, respectively (*Figure 1*). EBV-infected T/NK cells retain some characteristics of normal lymphocytes because they show homeostatic proliferation, but not infinite proliferation (in contrast to leukemic blasts). Although hypercytokinemia is sometimes severe during the administration of chemotherapy, it may be

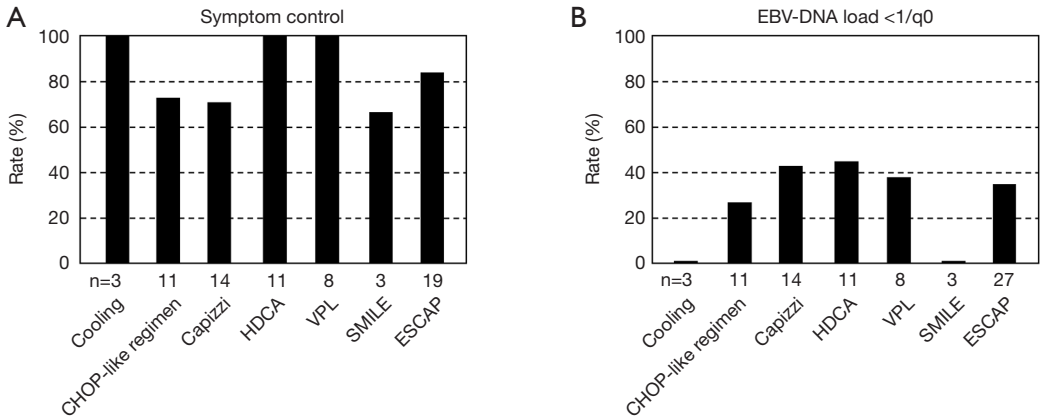

Figure 3 Effects of immunochemotherapy and multidrug chemotherapy on CAEBV. The effects of ESCAP and SMILE on CAEBV, which were administered for CAEBV between Jan 2007 and Dec 2015, were superimposed on those of other regimens previously reported in the literature (58). Cooling (step 1; immunochemotherapy) comprises PSL, CsA, and Etp. (A) The symptom control ratio indicates the total effect of CR, partial remission, and stable disease after chemotherapy. Patients with skin only CAEBV-associated diseases (HMB and sHV) were excluded. (B) Virological effectiveness was defined as an EBV-DNA load <1/10 after one course of each regimen. CAEBV, chronic active Epstein-Barr virus infection; PSL, prednisolone; CsA, cyclosporine A; Etp, etoposide; CR, complete remission; HMB, hypersensitivity to mosquito bites; sHV, systemic hydroa vacciniforme.

fatal during MAC for upfront HSCT in such patients. The cytokine storm (severe hypercytokinemia) was previously reported to be fatal, even after intensive chemotherapy (51). Therefore, the step-up strategy is preferable. The CHOP-like regimen needs to be considered as first-line chemotherapy, followed by more intensive chemotherapy and RIC-HSCT. Upfront HSCT is sometimes risky in this respect. The purposes and benefits of chemotherapy prior to HSCT are listed in *Table 3*.

The CHOP-like regimen is the most common 1st-line chemotherapy for lymphomas. THP-COP is the most frequently selected first-line chemotherapy in our institute (*Figure 1*) (49). CHOP and CHOEP are alternatives; however, pirarubicin is a widely used anthracycline in Japan because it is less cardiotoxic than doxorubicin (60,61). EBV-infected T/NK cells derived from most, if not all, patients are resistant to anthracycline due to their expression of p-glycoprotein (P-gp) (62). CsA down-regulates P-gp expression and restores T/NK-cell susceptibility to anthracycline (63). In addition, P-gp expressed in NK cells may not be the classical form, it may be a shorter form, which does not effectively export anthracycline (64). Therefore, the CHOP-like regimen may be more effective with CsA as described above or the COP regimen may be an alternative.

Second-line chemotherapy often contains cytosine arabinoside (CA) or L-asparaginase (65), and ESCAP has been the preferred choice at our institute since 2007. The effects of each chemotherapy are shown in *Figure 3* (58). Based on the EBV load as a molecular marker of measurable residual disease (MRD), 4 out of 92 patients achieved molecular complete remission (CR). Two patients received an additional single course of chemotherapy to maintain continuous CR without HSCT (patients #2 and #N03 in our previous studies) (19,66). The two other patients successfully underwent HSCT with their parents' and physician's choice (patients #362 and #668 in our previous study) (19).

Step 3 (reconstruction): allogeneic HSCT

The preparation of HSCT consists of three parts. The first part involves the pre-preconditioning (pre-RIC) of low-dose Etp and CA (LDEC). LDEC was historically innovated for better control of the leukemic-cell burden before HSCT (67,68), and for the better engraftment of upfront HSCT in benign diseases. However, regarding CAEBV, LDEC for 1–2 weeks has also provided a safe bridge to HSCT by controlling the tumor burden and disease activity.

The early stages of RIC consist of low-dose rabbit anti-thymocyte globulin (ATG; Thymoglobulin®, Sanofi, France; 1.25 mg/kg/d × 2 days) and preceding Mel. The aim of ATG is not to prevent graft-versus-host disease

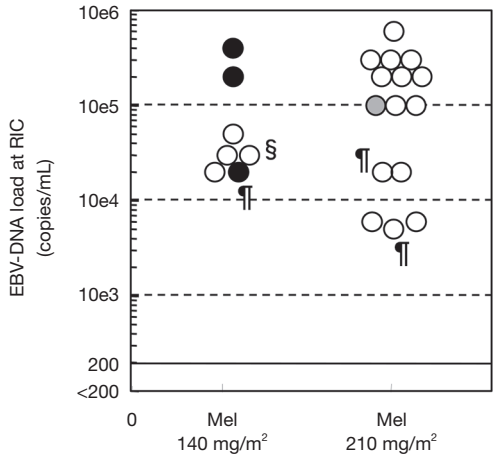

Figure 4 Impact of the EBV-DNA load and RIC intensity on CBT. A retrospective analysis of CBT performed between Jan 2010 and Dec 2017 (50). RIC with a total dose of Mel of 210 mg/m^2 (M210 RIC) resulted in the better engraftment of CBT than M140 RIC. All rejections were successfully rescued by second HSCT. However, the EBV-DNA load in PB at RIC had a negligible impact on 3-year event-free survival after CBT. Events: one relapse (47) and one TRM in the M140 RIC group, and two TRM in the M210 RIC group. Open circles: complete donor-type engraftment, closed circles: primary rejection, gray circle: late rejection (following viral infection 15 months after CBT), [§], relapse; [¶], TRM. EBV, Epstein-Barr virus; RIC, reduced-intensity conditioning; CBT, cord blood transplantation; Mel, melphalan; HSCT, hematopoietic stem cell transplantation; PB, peripheral blood; TRM, treatment-related mortality.

(GVHD), but to reduce recipient T-cell immunity in order to enforce donor-cell engraftment. ATG also reduces EBV-infected T/NK-cell numbers for better disease control (42). Preceding Mel 70 mg/m^2 (resulting in 210 mg/m^2 in total RIC) is administered for better engraftment in children and adolescents undergoing CBT after only 2 or 3 courses of chemotherapy. It is replaced by the systemic irradiation of 3 Gy with gonadal blockade in adults (50).

The main stage of RIC consists of fludarabine, Mel, and Etp. Mel ≤240 mg/m^2 is expected to preserve fertility in women (69). Etp was originally introduced to suppress antigen-presenting cells, thereby reducing GVHD and HLH after HSCT, and this concept was partially proven by a retrospective analysis (70). During RIC in patients with CAEBV, Etp provides a safety net for conditioning-associated HLH. Therefore, although Etp 100 mg/m^2/d is scheduled on days –3 and –2, it may be flexibly administered whenever HLH occurs (49).

Dose reductions in RIC according to a formula for organ dysfunction are reasonable. However, our RIC regimen has been fine-tuned. Therefore, excessive reductions may result in a higher rate of rejection or mixed chimerism.

Other considerations for clinical management

Virological CR

The main effector against CAEBV after HSCT is alloimmunity, not anti-EBV cytotoxic T lymphocytes (CTLs) (42). The EBV load (the MRD level) at RIC has a negligible impact on the success of CBT (*Figure 4*) (50). As described above, once CR is achieved after HSCT, the disease relapse rate is less than 5%. Furthermore, HSCT may be avoided when the EBV load is below the lower detection limit. Therefore, virological CR is beneficial, but not mandatory before HSCT.

Disease activity

Disease activity is important. Patients with mild symptoms may undergo successful HSCT. However, the prognosis of patients with severe disease activity even after chemotherapy is poor (OS rate <20%) (19,71). Among 12 patients with uncontrolled active disease, 4 died before HSCT, 3 died very early (d1, d3, and d4 after HSCT), and 3 died after emergent HSCT (19).

Caution is required when interpreting the findings of retrospective studies. In a previous study, 3-year OS rates in the upfront HSCT group (n=12), chemotherapy-HSCT group (n=47), and chemotherapy only group (n=20) were 82%, 65%, and 0%, respectively (14). However, a mild disease status may be included in the upfront HSCT group, a more active status in the chemotherapy-HSCT group, and progression before HSCT in the chemotherapy only group.

Advanced cases

CAEBV has a spectrum of disease severity, and there are two types of ANKL: *de novo* ANKL and ANKL transformed from CAEBV (26). ANKL may provide a more detailed understanding of advanced CAEBV. The OS rate of ANKL is <10% because it is mostly chemoresistant and mainly occurs in the elderly (72). However, recent findings indicate that OS is better at approximately 50% in CR patients (73). CAEBV is also generally a chemoresistant disease;

however, a transient improvement is often observed during myelosuppression after chemotherapy. The initiation of RIC under myelosuppression and before organ dysfunction progresses to irreversible organ failure may overcome CAEBV with an advanced status.

Perspectives

New drugs

The 3-step strategy has become the standard platform for the treatment of CAEBV. However, further advances are needed for a better prognosis and fewer late sequelae with new drugs and methods in the perspective of: (I) more sophisticated alternative approaches, (II) the better management of advanced disease, and (III) a radical cure other than HSCT. JAK 1/2 inhibitors, such as ruxolitinib, may provide an additive effect with PSL/CsA/Etp on CAEBV (74,75); however, it may not be sufficient as a single agent for EBV-associated hypercytokinemia/HLH (76). In contrast, emapalumab, a monoclonal antibody against interferon-gamma, achieved improvements in 65% of patients with HLH, including CR in 26%; however, single cytokine blockade does not appear to be sufficient for a multiple cytokine disease (77).

Ganciclovir is an antiviral agent that is effective against EBV-lytic infection, but not CAEBV. It is activated via phosphorylation with EBV protein kinase, which is not expressed during latent infection, including EBV-infected T/NK cells in CAEBV. Proteosome inhibitors, such as bortezomib, induce EBV protein kinase expression to change latent into lytic infection (78), and the combination of bortezomib and ganciclovir may exert cytoreductive effects on EBV-infected T/NK cells (79). Histone deacetylase inhibitors, such as romidepsin, also induce EBV-lytic infection (80). However, close monitoring is warranted because these lytic infection-inducible drugs may cause severe EBV reactivation (81,82).

Cellular therapy and immunotherapy

Immunological approaches are now being revisited 30 years after early treatment with interleukin-2 (44). Wang *et al.* reported that 3 out of 5 children with EBV-positive T-cell LPD achieved clinical remission following the infusion of HLA-haploidentical lymphocytes without HSCT (83). Although EBV-specific CTL therapy is currently being developed (84,85), the induction of CTLs targeting EBNA1 and latent membrane proteins (LMPs), which are proteins expressed in type-2 latencies, such as CAEBV, is limited (86). PD-1 and PD-L1 inhibitors, including nivolumab and pembrolizumab, exerted promising effects in a small case series (87,88). They were safely and effectively administered, but with careful monitoring for cytokine release syndrome in the short term and disease recurrence in the long term.

To conclude this manuscript as a narrative review, CAEBV is a rare disease, and clinical data are limited; therefore, future research is awaited.

Conclusions

CAEBV is a diverse disease that may rapidly progress. The three-step treatment strategy has provided a platform for the management of CAEBV. Some of the novel modalities described above may contribute to further improvements in the prognosis of these patients, particularly those with advanced CAEBV.

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