Current Diagnosis and Treatment Strategy for Chronic Active Epstein-Barr Virus Infection

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Abstract

Chronic active EBV infection (CAEBV) is a representative disease amongst a spectrum of EBV-associated T/NK-cell lymphoproliferative disease (LPD), with recently proposed diagnostic guidelines as follows; (1) persistent or recurrent infectious mononucleosis-like symptoms such as fever, swelling of lymph nodes, and hepatosplenomegaly, (2) an unusual pattern of anti-EBV antibodies with elevated levels of anti-viral capsid antigen and anti-early antigen, and/or evidence of increased EBV genome number in affected tissues, including the peripheral blood, (3) chronic illness which cannot be explained by other known disease processes at diagnosis. The prognosis of patients with CAEBV is very poor in both pediatric and adult patients. In the absence of effective therapy, almost all patients will die within 5–15 years from onset because of hepatic or cardiac failure, hemophagocytic syndrome, malignant lymphoma, opportunistic infections, or intracranial/gastrointestinal bleeding. To-date, investigational therapies for CAEBV have comprised immunoregulatory drugs and antiviral agents, all resulting in disappointing outcomes. Eleven years ago we sought to investigate a new therapeutic algorithm for CAEBV comprising sequential immunochemotherapy, combination chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) in an attempt to reduce and/or eliminate EBV-infected T/NK cells.

Introduction

Epstein-Barr virus (EBV), one of the eight known human herpesviruses, is ubiquitous and generally infects human individuals subclinically. However, EBV infection has been considered to be implicated in a variety of benign and malignant human diseases such as hematologic diseases (B-cell lymphoma/leukemia including African Burkitt's lymphoma, T/NK-cell lymphoma/leukemia, Hodgkin's disease, and post-transplant lymphoproliferative disease) and non-hematologic malignancies (nasopharyngeal carcinoma, gastric cancer, lymphoepithelial-like carcinoma, and smooth muscle sarcomas) (Kawa 2000).

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Following primary infection EBV can induce both replicative (productive/lytic) and latent (persistent) infections in lymphocytes. Latent EBV infection is linked to the development of a variety of lymphoproliferative disease (LPD), such as B-cell LPD and T-cell/natural killer cell (T/NK-cell) LPD (Kawa 2000, 2003). EBV-associated B-cell LPD is a well established phenomenon in patients with primary/secondary immunodeficiencies and in recipients of allogeneic transplants such as hematopoietic stem cell, heart, lung, liver, kidney and small intestine. These lymphoid proliferations, arising in the context of impaired T cell mediated immunity, range from reactive polyclonal B-cell hyperplasias without cytogenetic abnormalities to monoclonal malignant lymphomas (Heslop 2009).

In contrast to B-cell LPD, EBV-infected T/NK-cell LPD is usually observed in apparently immunocompetent persons. In the late 1980s, three different groups described T-cell lymphomas and T-cell LPD containing EBV DNA in patients with chronic active EBV infection (CAEBV) (Jones et al. 1988; Kikuta et al. 1988; Ishihara et al. 1989). Similarly, in 1989, we unexpectedly found evidence of EBV-infected NK-cell LPD in 5 of 7 studied patients with LPD of granular lymphocytes (Kawa-Ha et al. 1989). Since that time, a spectrum of EBV-associated T/NK-cell LPD has been increasingly recognized and more clearly defined: CAEBV, EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH), extranodal NK/T-cell lymphoma (nasal/nasal type), hypersensitivity to mosquito bites (HMB), hydroa vacciniforme (HV), and aggressive NK-cell leukemia. In spite of the heterogeneity of the clinical, phenotypic, and genotypic characteristics of these EBV+ T/NK-cell lymphoproliferations, many clinical and histological features are shared: (1) Fever and hepatomegaly/splenomegaly; (2) Extranodal lesions such as nose, skin, and digestive tract with a propensity for extra-nodal dissemination; (3) a high incidence of hemophagocytic syndrome (HPS); (4) Histopathological features of pleomorphism and angiocentricity/angioinvasion; (5) A mature phenotype of EBV-infected cells; (6) refractoriness to conventional treatments, and (7) higher prevalence in Asia and Central America (Iwatsuki et al. 1999; Kawa 2000; Kawa et al. 2001; Kasahara et al. 2001; Kimura 2006; Ohshima et al. 2008).

Epidemiology

Young children most likely acquire primary EBV infection from close contact that involves exchange of oral secretions via shared items such as toys, bottles, and utensils. In developing areas such as equatorial Africa and Southeast Asia, primary EBV infection is encountered in early childhood. At 2 years of age, approximately 80% of children in these regions are EBV seropositive, and by adolescence almost all are infected. In contrast, industrialized areas such as Europe and North America, primary infection is delayed, and half of adolescents are still EBV seronegative. Before the age of 10, primary infection is usually asymptomatic or produces an acute illness that is often not attributed to EBV. In adolescents and young adults, however, primary EBV infection frequently presents as infectious mononucleosis (IM). More recently, it became clear that acute/fulminant EBV-associated hemophagocytic syndrome/hemophagocytic lymphohistiocytosis (EBV-HPS/HLH) can occur in the context of primary infection. Historically, the age-defined seroprevalence of EBV in Japan was similar to those of developing countries, but the pattern has recently evolved to become more akin to that of industrialized countries (Kawa et al. 2002; Takeuchi et al. 2006; Okano 2009; Odumade et al. 2011).

Current Understanding of Epstein-Barr Virus-Associated Lymphoproliferative Disease

As described, initial infection is thought to occur in the oral (tonsillar) compartment. The host cells of EBV are mainly lymphocytes and epithelial cells. EBV attaches to B cells via binding of the viral gp350 protein to CD21 on B cells. EBV gp42 then

interacts with B-cell HLA class II molecules and triggers fusion with the host membrane. In epithelial cells, which lack CD21, the EBV BMRF-2 protein interacts with β1 integrins, and the EBV gH/gL envelope protein triggers fusion via interaction with αvβ6/8 integrins (Odumade et al. 2011). An important consequence of EBV infection in B cells is that they are induced to activate their growth program and trigger differentiation into memory B cells via the germinal center reaction. Infected memory B cells are released into the peripheral circulation, resulting in detectable levels of virus in the blood. The EBV-transformed B cells are controlled in vivo by HLA-restricted cytotoxic T-cell responses. Cytotoxic T cells in healthy carriers have multiple reactivities against different viral antigens. In contrast to lytic replication, episomal replication during the latent phase occurs via host DNA polymerase, and there is limited expression of EBV nuclear antigens (EBNAs; EBNA 1, 2, 3A, 3B, 3C), EBNA leader protein (EBNA-LP), and latent membrane protein (LMP1, 2a, 2b) gene products during latency. Other defense mechanisms include neutralizing antibodies (mostly against gp350), cytokines such as interferons, natural killer (NK) cells, and antibody-dependent cell-mediated cytotoxicity. Latency is the state of persistent viral infection without active viral production. Three distinct forms of EBV latent gene expression in B cells have been demonstrated in vitro and designated Latency I, II, and III. Burkitt's lymphoma is categorized as Latency I, characterized by expression of EBV-encoded RNA (EBER)-1 and -2 and EBNA-1. LMP-1, -2a, and – 2b are additionally expressed in Latency II (Hodgikin's disease and T/NK-cell LPD). Latency III is characterized by expression of all viral latent genes (IM, post-transplant LPD, primary effusion lymphoma, and AIDS-related lymphoma). By contrast to the well-characterised infection of B cells, however, the mechanism whereby EBV infects T/NK cells remains unclear.

Following primary EBV infection, immunoglobulin M (IgM) antibodies to viral capsid antigen (VCA) appears first, and subsequently IgG antibodies to both VCA and early antigen (EA) are noted. IgA antibodies to these antigens may also appear transiently at this time. The IgM anti-VCA response subsequently disappears during convalescence, whereas the IgG anti-VCA titer rises to a peak and then may fall slightly over the ensuing months to a stable steady-state level. Among anti-EBNA reactivities, an IgG response to the EBNA 2 protein appears in the acute phase, whereas an IgG response to EBNA 1 is not usually detectable until convalescence.

Increased antibody titers of IgG against VCA and EA or both indicate reactivation of EBV. However, EBV-specific serology alone is insufficient to evaluate EBV-associated LPD (EBV-LPD) (Kawa 2000; Okano 2009; Odumade et al. 2011).

As shown in Fig. 18.1, EBV-LPD can be classified into two types; B-cell LPD (B-LPD) and T/NK-cell LPD (T/NK-LPD), both with acute and chronic form. IM is an acute form of B-LPD characterized by fever, sore throat, and cervical lymphadenopathy, with a characteristic increase of atypical lymphocytes in the peripheral blood. In addition to these common features, hepatic, neurologic, and cardiologic complications occur with varying frequency. The majority of atypical lymphocytes are cytotoxic T cells (or rarely NK cells); thus vigorous immune responses of cytotoxic cells against EBV-infected B cells may result in clinical symptoms. Chronic form comprises a spectrum of disease including post-transplant LPD, AIDS-related LPD, diffuse large B-cell lymphoma (DLBCL) of the elderly, primary effusion lymphoma, and Burkitt's lymphoma.

EBV-HPS/HLH is a representative acute form of T-LPD. After primary infection, some patients develop prolonged fever, hepatosplenomegaly, pancytopenia, and coagulopathy. Morphologic examination of bone marrow and lymph nodes demonstrates prominent phagocytosis of erythrocytes and nucleated blood cells. Until recently, the pathogenesis of EBV-HPS/HLH was poorly understood, but recent studies have indicated that proliferation of EBV-infected T cells appears to be a primary feature of the disease, and

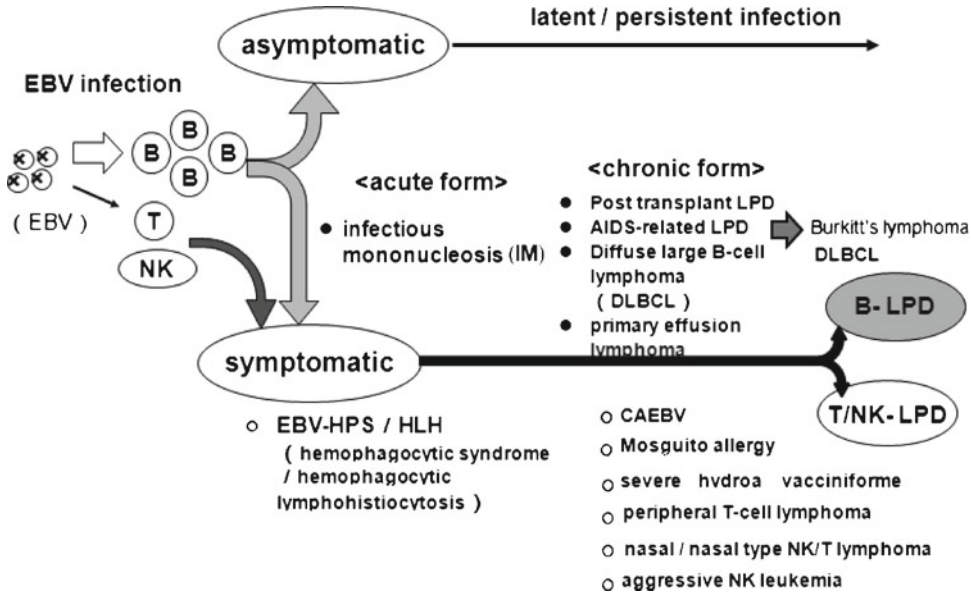

Fig. 18.1 Acute and chronic form of EBV infection. EBV-associated LPD can be classified into B-LPD and T/NK-LPD

unconstrained release of inflammatory cytokines (hypercytokinemia), such as interferon γ and tumor necrosis factor α, is a prominent feature of EBV-HPS/HLH (Kasahara et al. 2001). Because some cases have a fatal outcome, rapid diagnosis and initiation of immunochemotherapy (prednisone/dexamethasone, cyclosporine A, and etoposide) are recommended (Henter et al. 2007; Koyama et al. 2007). Stem cell transplantation should be considered if the patient responds poorly to immunochemotherapy or combined chemotherapy. Chronic form of T/NK-LPD comprises CAEBV, mosquito allergy, hydroa vacciniforme, peripheral T-cell lymphoma, nasal/nasal type NK-cell lymphoma, and aggressive NK-cell leukemia. Because no hereditary background in family members or antecedent immunodeficiencies were observed among these patients, EBV infection of T or NK cells may be a chance occurrence resulting in the development of LPD influenced by hitherto unknown co-factors. In parallel with the concept of HTLV-1-associated T cell leukemia/lymphoma, several lines of evidence support the notion of EBV-associated T/NK-LPD as a distinct disease entity (Kawa 2003).

Diagnosis of Chronic Active EBV Infection (CAEBV)

Over the past 20 years, confusion has persisted in relation to the diagnosis of CAEBV because of varying clinical manifestations, association with certain underlying diseases, and outcomes. With new diagnostic methods and improved knowledge about patient characteristics and outcomes, it has become possible to define more precisely the pathogenesis of CAEBV. Therefore we proposed a diagnostic guideline for CAEBV as described (Rickinson 1986; Okano et al. 2005). To improve the diagnostic specificity of this enigmatic disease, underlying diseases should be diagnosed accurately, and when the associated disease is defined, the name of each disease should be used rather than CAEBV. Additionally, the following supplemental findings and recommended specific laboratory tests are presented: (1) IM-like symptoms generally include fever, swelling of lymph nodes, and hepatosplenomegaly, (2) Anti-EBV antibodies with raised anti-VCA and –EA ordinarily consist of VCA-IgG $\gtrsim$ 1:640 and EA-IgG $\gtrsim$ 1:160; positive IgA antibodies to VCA and/or EA

are often demonstrated, (3) Recommended specific laboratory tests; (a) detection of EBV DNA, RNA, related antigens and clonality in affected tissue including the peripheral blood, (b) histopathological and molecular evaluation, (c) immunological studies including surface marker analysis of peripheral blood lymphocytes.

Treatment Strategy for CAEBV

CAEBV should no longer be considered an enigmatic disease, but rather can be defined as one of the representative EBV-associated T/NK-cell LPDs according to our current diagnostic criteria and the published experience from Japan. As shown in Fig. 18.2, CAEBV is a high-mortality, high-morbidity disease with life-threatening complications. Until recently, conventional therapies for CAEBV including antiviral drugs, immunomodulative agents such as immunoglobulins, interferon gamma, IL-2, corticosteroids or cyclosporine A have been tried without clear benefit, and a standard treatment approach has not been established (Ishihara et al. 1995). Therefore, we sought to investigate, 11 years ago, a new therapeutic algorithm for CAEBV comprising sequential immunochemotherapy, combination chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) in an attempt to reduce and/or eliminate EBV-infected T/NK cells (Kawa et al. 2011) (Table 18.1).

Following strict diagnostic characterization based on EBV-specific serologic findings, detection of EBV-infected cells, and the monoclonality of proliferating cells, all patients received immunochemotherapy comprising prednisolone 1–2 mg/kg/day, cyclosporine A 3 mg/kg/day and etoposide 150 mg/m^2/week to control disease symptoms as the first phase of therapy. Step 1 is crucial to render the disease inactive, which is achieved by targeting macrophages and suppressing activated T/NK cells and the associated hypercytokinemua. This therapeutic approach has recently become a gold standard for the treatment of HPS/HLH. Step 2 comprises additional chemotherapy agents, combined with cyclosporine, as follows: modified CHOP regimen (CY, pirarubicin hydrochloride, VCR and prednisolone), sequential high-dose

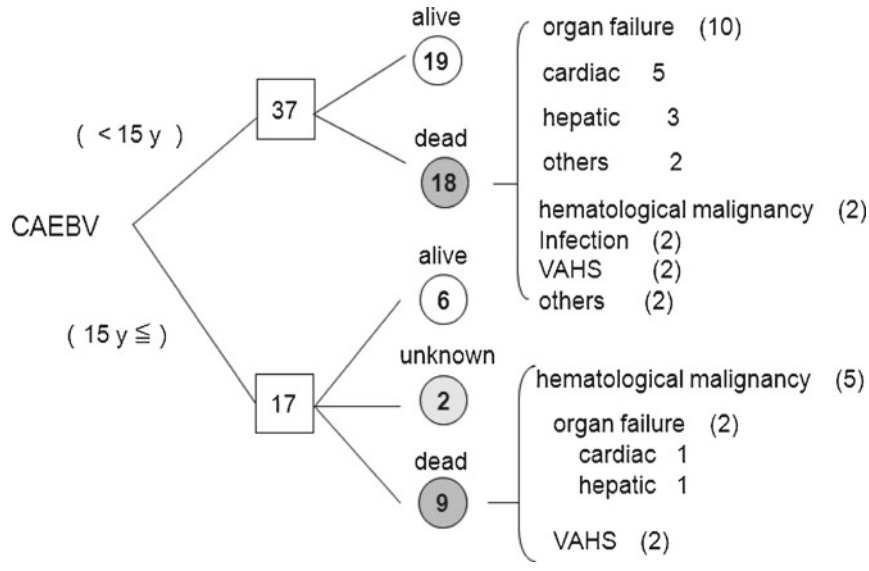

Fig. 18.2 Outcomes of 54 patients with CAEBV. Prognosis is very poor in both paediatric and adult patients. Nearly half of the patients are supposed to die within 4–5 years after onset (in 1994)

Table 18.1 Treatment strategy for chronic active EBV infection

Step 1 (cooling)	Suppression of activated T cells, NK cells and macrophages
	Prednisolone 1 to 2 mg/kg/day VP - 16 150 mg/m^2/w Cyclosporin 3 mg/kg/day
Step 2 (cytoreduction)	Elimination of EBV-infected T/NK cells
	Combination chemotherapy
	(A) Modified CHOP (CY 750 mg/m^2 day 1, pirarubicin 25 mg/m^2 days 1 and 2,VCR 2 mg/m^2 day 1 and PSL 50 mg/m^2 days 1–5)
	(B) Capizzi (ara-C 3 g/m^2 every 12 h × 4, L-asp 10,000 U/m^2 × 1(i.v. after 4 h post-ara-C). PSL 30 mg/m^2 days 1 and 2)
	(C) HDCA(ara-C 1.5 g/m^2 every 12 h × 12 and PSL 30 mg/m^2 days 1–6)
	(D) VPL(VP-16 150 mg/m^2 day 1, PSL 30 mg/m^2 days 1–7, and L-asp 6,000 U/m^2 days 1–7)
	(E) ESCAP (VP-16 150 mg/m^2 × 1, ara-C 1.5 g/m^2 × 2/day × 4, L-asp 6,000 U/m^2/day × 5, PSL 30 mg/m^2/day × 9)
Step 3 (reconstruction)	Hematopoietic SCT(HSCT)

Abbreviations: *HDCA* high-dose ara-C, *HSCT* hematopoietic SCT, *L-asp* L-asparaginase, *NK* natural killer, *PSL* prednisolone

ara-C (HDCA; ara-C 3 g/m^2 × 2/day × 4, L-asparaginase 6,000 U/m^2 × 1), HDCA (ara-C 1.5 g/m^2 × 2/day × 6), VPL (VP-16 150 mg/m^2 day 1, prednisolone 30 mg/m^2/day × 7, L-asparaginase 6,000 U/m^2/day × 7) and ESCAP (VP-16 150 mg/m^2 day 1, ara-C 1.5 g/m^2 × 2/day × 4, L-asparaginase 6,000 U/m^2/day × 5, prednisolone 30 mg/m^2/day × 9), which is intended to eradicate EBV-infected T/NK-cells. All patients received at least one of these regimens, and in the event of a < 1 log reduction of EBV load, a further cycle was repeated or a different combination chemotherapy regimen was instituted before proceeding to allo-HSCT.

Disease status before allo-HSCT was assessed based on clinical features and EBV load and consequently classified as either active or non-active. Active disease was defined by the existence of symptoms and signs such as fever, persistent hepatitis, lymphoadenopathy, hepatosplenomegaly, pancytopenia and/or progressive skin lesions alongside an elevated EBV load in the peripheral blood. In the event of active persistent disease during chemotherapy, HSCT was planned as soon as possible before progression to a fulminant clinical course. Although our experience is that HDCA is most effective in reducing EBV DNA load, the efficacy of chemotherapy, as judged by clinical features and degree of liver dysfunction, was similar among the different combination chemotherapies. By using this approach we achieved a non-active disease status before allograft conditioning in ~66% of patients. In a small number of patients whose EBV load became undetectable after step 2, a durable CR without allogeneic transplantation was achieved. Therefore, more effective treatment strategy, including new combination chemotherapy as well as other approaches, remains to be established (Koyama et al. 2005; Kawa et al. 2011). The use of EBV-specific cytotoxic T cells might be considered in step 2 (Heslop 2009).

Since the first case report of successful allo-HSCT (Okamura et al. 2000), thus far, we have performed allo-HSCT for 41 patients with CAEBV. In our latest report we have compared the outcomes of 29 patients who received allo-HSCT using either myeloablative conditioning (MAC) allo-HSCT (MAST) or reduced-intensity conditioning (RIC) allo-HSCT (RIST) between August 1997 and December 2008. Conditioning regimens were assigned as myeloablative or reduced intensity as follows. MAC consisted of total body irradiation (TBI) (12 Gy in 6 fractions), etoposide (900 mg/m^2 × 1 dose) and CY (120 mg/kg in 2 doses) or melphalan (210 mg/m^2 in 2–3 doses), and RIC included fludarabine

(~180 mg/m^2 in 5–6 doses) and melphalan (140 mg/m^2 in 2 doses) or CY (120 mg/kg in 2 doses), with/without antithymocyte globulin and low-dose irradiation.

The application of GVHD prophylaxis was variable because of the different stem cell sources and degree of HLA disparity. Cyclosporin (3 mg/kg daily by continuous infusion) was used for HLA-matched related bone marrow transplant (BMT), and tacrolimus (0.02 mg/kg daily by continuous infusion) was used for CD34-positive stem cells transplant. In case of HLA-matched unrelated BMT and HLA-mismatched unrelated cord blood transplant, tacrolimus and a short course of MTX (7.5 mg/m^2 on days 1, 3 and 6) were used. In other situations, GVHD prophylaxis was intensified by adding anti-T lymphocyte globulin or antithymocyte globulin (ATG, horse). Treatment related mortality (TRM) was defined as any death that occurred while the patient was in remission.

The median age of 29 patients at onset was 10 years (ranging from 1 to 38 years), and peripheral blood EBV load (whole blood) in tested patients ranged from 10^3 to 10^7 copies/ml ($<2\times10^2$ copies/ml in healthy volunteers). Thirteen patients were defined as having T-LPD, 13 patients had NK-LPD, and 3 were classified as T- and NK-cell type. Eleven of the 29 patients received MAC and 18 patients received RIC. Stem cell sources comprised 3 CD34, 2 related BM and 6 unrelated BM in the MAST group, and 4 related BM, 8 unrelated cord blood, 2 CD34, 2 related peripheral blood and 2 unrelated BM in the RIST group.

Acute GVHD (aGVHD, grades II to IV) was observed in 6/9 and chronic GVHD (cGVHD) was observed in 2 patients; one extensive type and one limited type in the MAST group. Similarly, in the RIST group, aGVHD (II to IV) was observed in 11/16, and 3 patients (3/17) developed cGVHD; one extensive type and two limited type. Thus, there was no significant difference in aGVHD ($p=0.915$) and cGVHD ($p=0.835$) between MAST group and RIST group. Although the proportion of patients with active and non-active disease status before the preconditioning was similar in the two groups, a higher incidence of TRM was observed in the Mast group. The incidence of TRM in the Mast group was 5/11 (45%), accounted for by 2 deaths with veno-occlusive disease, 1 infection-associated hemophagocytic syndrome, 1 renal failure (BK virus) and 1 GVHD. Six patients were continuous CR from 68 to 134 months, corresponding to a 3-year event free survival (EFS) and overall survival (OS) of $54.5\pm15.0\%$ for both outcomes. In contrast, the incidence of TRM in the RIST group was 1/18 (5.6%), because of a subarachnoid hemorrhage. Two patients experienced graft failure and mixed chimerism, respectively, who both subsequently received a successful second RIST. A third RIC allo-HSCT was performed for a patient who had failed engraftment twice at a previous hospital where RIC allo-HSCT was conducted without chemotherapy before the transplant preconditioning. The 3-year EFS for the RIST group was $85.0\pm8.0\%$ and the 3-year OS was $95.0\pm4.9\%$ (Fig. 18.3).

Although the number of patients was small, a higher incidence of TRM in the MAST group (3/5) and a lower incidence in the RIST group (1/10) were also reported (Gotoh et al. 2008). In contrast to our data, however, a relatively high relapse rate was observed in their RIST group compared with our cohort (30 vs 11%). Although data of preceding treatments before the preconditioning were not stated in their paper, it may be that our strategy, including immunochemotherapy and combination chemotherapy before the preconditioning, may contribute to the superior outcomes. Sato et al. (2008) collected 42 cases of CAEBV who underwent allo-HSCT (31 MAST and 11 RIST) between March 1997 and October 2003 in Japan, and their EFS was 56%. These two reports suggest that a longer interval between disease onset and HSCT is associated with a higher mortality rate, consistent with the natural history of CAEBV patients who tend to have more life-threatening complications and comorbidities as their clinical course progresses. In this study the median duration from disease onset to HSCT was shorter in RIST group (14.5 months) than in Mast group (3 years). This may potentially confer a survival advantage to the RIST group. Over the past decade, a range of RIC protocols have been designed with the aim of reducing

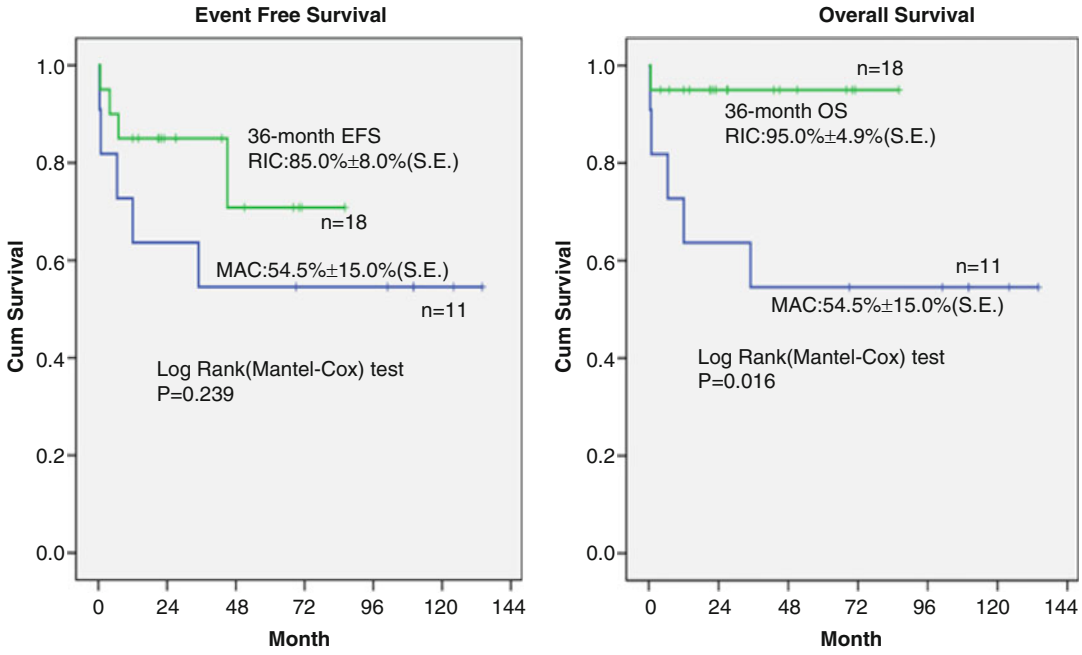

Fig. 18.3 Outcome of CAEBV patients after MAST and RIST. *MAST* myeloablative conditioning stem cell transplant (SCT), *RIST* reduced-intensity conditioning

toxicity while exploiting the graft-versus-tumor effect (Shimoni et al. 2007). Our first patient with CAEBV who underwent RIST instead of MAST was a 31-year-old woman. After receiving chemotherapy consisting of CHOP, sequential HDCA and HDCA, a reduction in the peripheral blood EBV DNA load reached the lower threshold of detection. We then performed a related BMT using RIC consisting of fludarabine and melphalan from an HLA-identical sibling donor. Her post transplant clinical course was uneventful, and she menstruated again 3 months after HSCT (Sakata et al. 2004). This case encouraged us to continue RIST with fludarabine and melphalan for the treatment of CAEBV. Because the outcome of patients who received RIST was excellent, all of the additional 12 patients until January 2011 were similarly treated with excellent outcomes (OS of 32 RIST; 93%).

Recipients of allo-HSCT sometimes show an increased EBV load, which may progress to EBV-associated LPD. These complications have been linked to (1) ex vivo or in vivo T-cell depletion, (2) unrelated donor, (3) HLA-mismatched donor, (4) anti-thymocyte/lymphocyte globulin, (5) reduced-intensity conditioning, and (6) UCBT (Kawa et al. 2007). In the present study, two-thirds of the RIST group had these high risk factors. Recently, UCBT has become a valuable alternative for patients who require HSCT but lack a suitable donor, and 8 UCBT were included in our RIST group. Brunstein et al. (2006) recently reported a high incidence of EBV-associated B-cell LPD after UCBT when RIC and ATG were combined (ATG+21% vs ATG- 2%). Although 6 of the 8 UCBT in our study were treated with RIC and ATG/ALG, none developed B-cell LPD. Possible explanations for the difference include: (1) An ATG/ALG dose equivalent to 1/2–1/4 of standard doses, (2) careful monitoring of EBV load and EBV antibody titers during and after UCBT. In the case of UCBT, the donor cells are assumed to be EBV negative. Therefore, EBV infection after UCBT constitutes a reactivation of the endogenous EBV strain or a new primary infection with an exogenous EBV strain (Sawada et al. 2011). We have assessed 57 recipients of 78 UCBT undertaken prior to 2008 to determine EBV serology. Among the 57 patients, 46 were EBV seropositive before UCBT. Following UCBT, 19 of the 46

seropositive recipients became EBV seronegative. Thus, EBV infection after UCBT can be considered as two types; endogenous transmission and exogenous re-infection. Serial monitoring of the EBV load and EBV serologic evaluation are required after UCBT for the early prediction and treatment of active EBV infection.

In conclusion, 29 patients with CAEBV were transplanted employing a variety of stem cell sources. Six of the 11 patients with MAST and 15 of the 18 patients with RIST were successfully treated and continue in remission. Two patients of the 18 RIST group failed to engraft, but were successfully treated with a second RIST. One of the 18 RIST patients received a successful third RIST after failing RIC allo-HSCT twice at a previous hospital. Overall survival was 54.5% (6/11) in the MAST group and 95% (17/18) in the RIST group. The excellent outcomes in the RIST group may be explained by (1) early intervention after the disease onset, (2) low incidence of TRM, (3) combination chemotherapy prior to the transplant preconditioning to reduce/eliminate EBV-infected T/NK cells, (4) regular monitoring of EBV load and serologic evaluation after HSCT to predict and treat active EBV infection.

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