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Optimal Treatment for Chronic Active Epstein-Barr Virus Disease

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Epstein-Barr virus (EBV) is a ubiquitous virus that infects at least 95% of the population. Most persons are infected during infancy and early childhood and are asymptomatic or have nonspecific symptoms (1). Infection of adolescents and young adults with EBV often results in infectious mononucleosis with fever, lymphadenopathy, sore throat, and splenomegaly. Additional signs and symptoms can include fatigue, headache, hepatomegaly, and rash. EBV is also associated with a number of malignancies including Hodgkin's disease, B cell lymphomas, and nasopharyngeal carcinoma. With the exception of the latter disease, EBV is present in B cells where it can result in lytic infection, with production of virus particles, or a latent infection with various patterns of viral gene expression. EBV can result in fatal infections in some hosts. Males with the X-linked lymphoproliferative disease often develop fatal infectious mononucleosis during primary EBV infection. Those who survive the disease often have hypogammaglobulinemia and are at increased risk for developing B cell lymphomas.

Chronic active EBV (CAEBV) disease is a very rare disease in the United States and Europe, but occurs more frequently in Asia and South America. Unlike most EBV disorders, the vast majority of cases of CAEBV in Asia and South America are due to EBV present in either T cells or NK cells. In contrast, EBV is often in B cells in patients with CAEBV in the United States. This disease is defined as (a) beginning with an acute EBV infection, having markedly elevated antibodies against EBV, or having a markedly elevated EBV DNA level in the blood (<300 copies/ug DNA), (b) histologic evidence of organ infiltration with virus-infected cells, and (c) detection of EBV protein or nucleic acid in tissue (2,3). CAEBV has been reported to be a clonal, oligoclonal, or polyclonal disease (4).

Most patients with CAEBV present with fever, liver dysfunction, and splenomegaly. About half of patients have lymphadenopathy, thrombocytopenia, and anemia (3). Other frequent symptoms (occurring in 20–40% of patients) include hypersensitivity to mosquito bites, rash, hemophagocytic syndrome, and coronary artery aneurysms. Less common features are calcification of basal ganglia, oral ulcers, lymphoma, interstitial pneumonia, and central nervous system disease. The presence of thrombocytopenia, onset at age 8 or older, and infection of T cells with EBV was associated with a poorer prognosis (5). Death is frequently due to liver failure, malignant lymphoma, or opportunistic infections.

Several immunologic abnormalities have been noted with CAEBV. Patients with T or NK cell disease frequently have elevated levels of pro- and anti-inflammatory cytokines including interleukin (IL)-1 β , interferon (IFN)- γ , IL-10, IL-13, IL-15, tumor necrosis factor (TNF)- α , and transforming growth factor (TGF)- β (4,6). Impaired natural killer (NK) cell activity, lymphokine activated killer (LAK) activity, and EBV-specific cytotoxic T lymphocyte activity were reported in 11 patients with CAEBV when compared to controls (7). EBV-specific CD8 + T cells are often very low or undetectable in CAEBV (8) and impaired cytotoxic T cell responses to EBV-infected NK cells have been reported (9). In one report, EBV-specific

cytotoxic T lymphocyte activity was impaired both in children with CAEBV and their parents (10).

The etiology of chronic active EBV is unknown. Early work suggested that the disease might be due to mutant strains of EBV that are impaired for latency and might only result in lytic infection (11). However, a followup study showed that the same lytic strain was present in controls (12). Attention has focused on a host cell genetic abnormality. In one large study 50% of patients had chromosomal abnormalities (3). CAEBV shares some features with X-linked lymphoproliferative disease, which is due to a mutation in SAP (SLAM associated protein). Many patients with CAEBV develop hemophagocytic syndrome; some patients with familial hemophagocytic lymphohistiocytosis have mutations in perforin. Therefore, attention has focused on the SAP and perforin genes as possible causes of CAEBV. To date, no cases of CAEBV have been associated with mutations in SAP (3,13, Cohen et al unpublished data), while one case was reported that was due to mutations in both alleles of the perforin gene (14). Hemophagocytic syndrome was noted in this latter case and the patient had an immature form of perforin and impaired cytotoxic T lymphocyte (CTL) activity based on an in vitro assay. Transcriptional profiling of cells from patients and controls showed that 3 genes- guanylate binding proteins 1 and 5, and tumor necrosis factor-induced protein 6- were upregulated in patients with CAEBV (15).

Numerous agents have been tried for the treatment of CAEBV. While anecdotal reports suggested that antiviral therapy (e.g. acyclovir, ganciclovir, vidarabine) might be effective in some cases of CAEBV (16,17,18), antiviral therapy is generally ineffective for this disease. These agents inhibit the viral DNA polymerase and therefore inhibit replication of EBV in lytically infected cells that express the viral polymerase. EBV-infected NK or T cells from patients with CAEBV generally express latent (EBV nuclear antigen [EBNA]-1, latent membrane protein [LMP]-1, LMP2A), but not lytic (EBV BZLF1, glycoprotein 350) viral gene transcripts (4). Replication of latent EBV in proliferating B cells does not require the viral DNA polymerase, and therefore antiviral therapy is usually ineffective. Immunoglobulin therapy, which can neutralize cell-free virus, has not been successful.

Immunosuppressive agents, such as corticosteroids and cyclosporine, are often used to temporarily reduce symptoms in patients with CAEBV. These agents have been successful for treating hemophagocytic syndrome which is a frequent complication of CAEBV (19). However, the underlying disease must also be treated and these agents have not been successful in curing patients with CAEBV (20). Immunosuppressive agents can inhibit the immune response to EBV and may allow virus-infected cells to proliferate further.

Immunomodulatory therapy has also been tried for the treatment of CAEBV. IFN- α (21) and IFN- γ (22) have been reported to induce remissions in some patients with CAEBV; however, long term follow-ups have not been reported. One patient was reported to respond to IL-2 (23). However, most patients have not responded to these therapies (20). Cytotoxic chemotherapy has also been used to treat CAEBV. A variety of agents have been used including cyclophosphamide, anthracyclines, vincristine, etoposide, and prednisone. In most cases, these agents at best result in a temporary effect, but are not curative and the disease continues to progress over time.

Immune cell therapy has been successfully used in the treatment of EBV lymphoproliferative disease that occurs after solid organ or hematopoietic stem cell transplantation. Autologous LAK cells, lymphocytes from HLA-identical siblings, and autologous EBV-specific CTLs have been used successfully to treat patients with posttransplant lymphoproliferative disease in solid organ transplant recipients. Autologous EBV-specific cytotoxic T cells were used to treat persistent active EBV in one study (24). This disease was defined as fever, fatigue,

lymphadenopathy, elevated EBV antibody titers, and increased levels of EBV DNA in blood. However, tissue pathology was not required for a diagnosis, the disease was likely due to EBV in B cells, and the course was much less severe than most cases of CAEBV. Autologous EBV-specific CTLs were successful in 4 of 5 cases, with a 6 to 36 month follow-up.

Infusions of EBV-specific cytotoxic T lymphocytes from an HLA-identical sibling into a boy with CAEBV resulted in transient decreases in EBV DNA in the plasma and decreases in serum levels of TNF- α ; however, the patient died of an infection 4 weeks after the last infusion (25). In another report (26), a patient with CAEBV received 13 doses of LAK cells followed by 4 doses of autologous CTLs. While the patient had a transient improvement with reduced fever and reduction of the viral load, pancytopenia persisted. A second patient with NK cell CAEBV received 4 doses of autologous CTLs; however, the viral load and hepatic dysfunction did not improve (26). The authors concluded that the effect of these therapies was very limited.

Matched related myeloablative (27,28), matched related nonmyeloablative (29,30,31), matched unrelated myeloablative (31,32), and cord blood stem cell transplants (33,34) have all been reported to be successful in case reports of CAEBV. It is important to note that most reports of transplantation for CAEBV are case reports describing one or a few patients, and as such often report successful cases. In the largest series from a single institution, 8 of 15 patients with CAEBV were alive at a median followup of 40 months (31). Seven patients died at a median of 3 months after transplant; three patients died of transplant related causes, 3 died due to relapsed disease, and 1 died with encephalomyelitis. Older age at diagnosis, higher EBV DNA load in the plasma at diagnosis, and a longer time between onset of infection and diagnosis of CAEBV correlated with a poorer prognosis after transplant.

The paper in this issue of Pediatric Transplantation (35) describes two patients with CAEBV. Both patients had low EBV-specific CTL activity, but normal NK cell activity prior to transplant. One patient had EBV in T cells and the other had virus in NK cells. Both patients were transplanted within 6 months of the diagnosis of CAEBV. After bone marrow transplantation both patients had an excellent response with rapid recovery of EBV-specific CTL activity and a precipitous fall in the level of EBV DNA in the blood. Uehara et al. (29) and Yoshida et al. (30) reported patients who underwent allogeneic nonmyeloablative stem cell transplants for CAEBV; while EBV-specific CTL activity was not reported prior to transplantation, EBV-specific CTLs were detected 120 days (30) and one year (29) after transplant.

How might transplantation cure CAEBV? Cytotoxic chemotherapy might reduce the burden of EBV-infected lymphocytes, might kill suppressor (or regulatory) T cells, or might make space in the marrow for the new stem cells. Transplanted stem cells can kill the remaining EBV-infected lymphocytes and provide a new immune system capable controlling the virus.

What does the future hold in store for patients with CAEBV? Gotoh et al. (31) reported that patients with CAEBV may have higher rates of transplant-related complications than other patients due to multi-organ failure. Thus, safer alternatives to transplantation should be developed. More recent studies with EBV-specific CTLs target specific viral proteins. T or NK cells from many patients with CAEBV express EBV EBNA-1, LMP1, and LMP2; however, the cells may not express EBNA-2 (4) or the EBNA-3 proteins (36). The EBNA-3 proteins are the immunodominant epitopes recognized by most EBV-specific CD8+ T cells in healthy persons (37). Therefore, CTLs specific for EBV LMP1 and LMP2 may be more effective than total EBV-specific T cells (that predominantly recognize EBNA-3) for patients with CAEBV. LMP2-specific T cells have recently been used to treat patients with EBV-positive lymphomas which express EBNA-1, LMP1, LMP2, but not EBNA-2 or EBNA-3

(38). Thus, treatment directed against specific EBV proteins may provide a safer and more specific therapy for CAEBV in the future.

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