Epstein-Barr Virus Infection and Lymphoproliferative Disorder After Hematopoietic Cell Transplantation

Yazhen Zhong, RN, ANP, AOCNP®

Common herpes viruses such as Epstein-Barr virus (EBV) cause infection and disease after hematopoietic cell transplantation (HCT). Post-transplantation lymphoproliferative disorder following allogeneic HCT is a rare but life-threatening disease, mostly associated with EBV-infected B cells. Anti-CD20 monoclonal antibodies (e.g., rituximab) target normal and infected B cells and further suppress the patient’s immune system. This article describes the development of cellular therapies by infusing virus-specific cytotoxic T lymphocytes via IV into patients to create an adoptive immune system for specific viral suppression.

Yazhen Zhong, RN, ANP, AOCNP®, is an advanced practice nurse at the University of Texas MD Anderson Cancer Center in Houston. The author takes full responsibility for the content of the article. The author did not receive honoraria for this work. No financial relationships relevant to the content of this article have been disclosed by the author or editorial staff. Zhong can be reached at yazhen_zh@yahoo.com, with copy to editor at CJONEditor@ons.org.

Digital Object Identifier: 10.1188/12.CJON.211-214

M s. M, a 34-year-old woman, was diagnosed with Hodgkin lymphoma in 2000. She received standard chemotherapy and radiation treatment and had a disease recurrence in her right femur within a few months. She received additional radiation and underwent autologous stem cell transplantation in 2001. She achieved complete remission until early 2009, when she was diagnosed with treatment-related acute myeloid leukemia. Ms. M had chromosomal abnormality with deletion 7, inversion 9, and trisomy 21. After receiving standard induction and consolidation chemotherapy, she achieved morphologic remission but had persistent chromosomal abnormality. Ms. M then underwent double cord blood stem cell transplantation in October 2009 with conditioning chemotherapy and antithymocyte globulin.

The immediate post-transplantation course was uneventful except for mild side effects including nausea, fever, and oral thrush. The engraftment occurred at day 26. At about 50 days following transplantation, Ms. M developed dysuria, hematuria, and mild gastrointestinal graft-versus-host disease. She was started on graft-versus-host disease treatment. Adenovirus was found in the urine culture, and she was managed symptomatically with IV fluid and medications for pain and dysuria. Adenovirus then was isolated in her stool. Ms. M was offered cytotoxic T lymphocyte (CTL) treatment for adenovirus infection, but she refused it at that time because she was concerned about the side effects. One month later, adenovirus was positive in her blood. Ms. M was started on cidofovir (1 mg/kg) and probenecid every other day for four weeks. All the viruses were monitored and the infection seemed to be controlled, although Ms. M had been hospitalized several times for fevers, pneumonias, diarrheas, and seizures, with evidence of posterior reversible encephalopathy syndrome on magnetic resonance imaging (MRI) during the next six months.

In August 2010, Ms. M was admitted for fever and tonsillitis, and she had noticed neck lymphadenopathy. Fine needle biopsy of the neck lymph node revealed Epstein-Barr virus (EBV)-positive post-transplantation lymphoproliferative disorder (PTLD). EBV DNA load via quantitative polymerase chain reaction assay was 100,826 copies/ml plasma. At the author’s institution, fewer than 400 copies/ml plasma indicates EBV low positivity. Standard rituximab treatment was started at a dose of 375 mg/m². Ms. M received weekly rituximab for four weeks. EBV DNA load was monitored weekly, and the level declined but rebounded two weeks after treatment completion. PTLD subsequently was detected in biopsies of the rectum, new skin papule, and stomach ulcers. In September 2010, a bronchoscopy revealed adenovirus, aspergillus, and candida infections, and a right lung nodule biopsy showed EBV-positive PTLD, monoclonal, consistent with diffuse large B-cell lymphoma. Ms. M received antifungal agents, and CTL treatment was reintroduced.

Ms. M was enrolled in a protocol of trivirus-specific CTL for treatment in September 2010. That CTL was developed to target cytomegalovirus (CMV), adenovirus, and EBV infections. Per protocol, Ms. M received a total of five doses of CTL between September 2010 and March 2011, and all three viruses were monitored. Ms. M had no indication of CMV infection, and adenovirus infection seemed to be controlled during that period of time. After the first dose of CTL infusion, weekly EBV DNA load in the blood improved greatly from 19,000 copies/ml to fewer than 400 copies/ml plasma, which is defined as low positivity and considered a complete response. However, EBV-positive PTLD had involved Ms. M’s left lungs in October 2010 and bone marrow in November 2010. During the same time, Ms. M developed seizures and MRI of the brain showed evidence of multifocal lesions that were not
biopsied secondary to low platelet counts. Ms. M received three more doses of CTL from December 2010 to January 2011 in the interval of at least two weeks apart.

In February 2011, a computed tomography scan of the chest showed Ms. M had increased lung infiltrates, and bronchoscopy showed adeno virus infection. High-dose cidofovir (5 mg/kg) was initiated per recommendations from the infectious disease specialist. Ms. M further developed mental status change, which was suspected for viral encephalitis, and she was treated with foscarin. The fifth dose of CTL was given in March 2011 in the hope of treating disseminated adeno virus infection and PTLD. Later in that month, Ms. M was transferred to the intensive care unit for respiratory failure and seizures. She was intubated for about two months and supported with multiple antimicrobials. She died in May 2011 with multiple organ failure.

Epstein-Barr Virus Infection

EBV, a member of the herpes virus family, was first identified in tissue obtained from a patient with Burkitt lymphoma (Epstein, Achong, & Barr, 1964) (see Figure 1). Typically, the virus is transmitted easily through the saliva. According to the Centers for Disease Control and Prevention (CDC, 2011), many children are infected with EBV but usually are asymptomatic. When EBV infection occurs during adolescence and young adulthood, it causes infectious mononucleosis 35%–50% of the time; the symptoms self-resolve without treatment (CDC, 2011). Up to 95% of American adults aged 35–40 have been infected with EBV; the virus remains latent and establishes lifelong dormant infection in B lymphocytes, which is believed to be associated with the development of Burkitt lymphoma and nasopharyngeal carcinoma when the host immune system is disrupted (CDC, 2011).

Post-Transplantation Lymphoproliferative Disorder

The cumulative incidence of EBV-positive PTLD after umbilical cord blood transplantation is 2% at two years (Barker et al., 2001). The risk of developing PTLD for allogeneic hematopoietic cell transplantation (HCT) recipients is about 1% (Reddy, Rezvani, Barrett, & Savani, 2011); however, PTLD can progress rapidly to a life-threatening and frequently fatal condition (Gross, 2010). Almost 100% of PTLD in allogeneic HCT recipients results from Epstein-Barr virus (Gross, 2010). The development of PTLD is a complex and multifactorial process. In the majority of allogeneic HCT recipients, EBV-associated PTLD is of a donor origin (Gross, 2010). The four high-risk factors for developing PTLD are patients being aged 50 years or older at time of transplantation, T-cell depleted graft, antithymocyte globulin use, and unrelated or human leukocyte antigen-mismatched graft (Curtis et al., 1999; Landgren et al., 2009). In addition, patients with no risk factors had a cumulative incidence of 0.2% versus 8.1% for those with three or more risk factors (Landgren et al., 2009).

Characteristics

PTLD represents a heterogeneous group of lymphoproliferative disorders ranging from reactive, polyclonal hyperplasia to aggressive non-Hodgkin lymphoma (Reddy et al., 2011). Clinical presentations may be nonspecific and resemble an infectious mononucleosis–like illness with fatigue, fever, and lymphadenopathy. Disseminated lesions involve organs and systems beyond the lymph nodes, such as the liver, kidney, bone marrow, gastrointestinal tract, liver, and central nervous system (Allen, 2010). Generalized lymphadenopathy, respiratory failure, and elevated liver function tests usually are associated with rapidly progressive multiple organ failure and death (Reddy et al., 2011).

Diagnostic Evaluation

Preiksaitis (2010) found that Epstein-Barr virus DNA load in peripheral blood via quantitative polymerase chain reaction amplification represents a potentially powerful tool for surveillance in PTLD prevention, monitoring response to PTLD treatment, and predicting disease relapse. However, EBV DNA load by itself has poor specificity for the diagnosis of PTLD (Preiksaitis, 2010). Allen (2010) indicated that tissue biopsy with histopathologic examination (in situ hybridization or immunohistochemistry) remains the gold standard for the diagnosis of PTLD. EBV-encoded RNA in situ hybridization is the most sensitive tool for detecting virus in tumors (Reddy et al., 2011). Evidence-based guidelines recommend weekly screening of EBV DNA load for at least three months in high-risk allogeneic HCT recipients (Styczynski, Reusser, et al., 2009). In this article, high-risk patients are defined as those who received unrelated, mismatched, or T-cell depleted transplantations.

In addition to EBV-specific tests, thorough diagnostic evaluation may include complete blood counts with differentials, liver and renal function tests, serum electrolytes, calcium, uric acid, lactate dehydrogenase, serum immunoglobulins, chest radiography, and computed tomography scan of the chest, abdomen, and pelvis (Allen, 2010). Additional selective tests such as lumbar puncture, bone marrow biopsy, MRI of the brain, endoscopy, and positron emission tomography may be ordered depending on clinical presentations (Allen, 2010).

Current Management

Limited treatments are available for EBV control, as current antiviral drugs do not...
appear to be effective. The limitation with antiviral drugs is that EBV-infected B cells are in a latent phase, whereas the antiviral drugs block only actively replicating herpes viruses and do not affect the growth of cells that have transformed already (Bollard, Kuehnle, Leen, Rooney, & Heslop, 2004). Cellular therapy with EBV-specific CTLs has become more popular since 1995 when they were used for prophylaxis in patients at high risk for developing PTLD (Wagner, Rooney, & Heslop, 2002).

The anti-CD20 monoclonal antibody rituximab has been used as preemptive therapy for EBV infection and treatment for PTLD in allogeneic HCT recipients since it first was studied by Kuehnle et al. (2000). Initial response rates range from 55%–100% in many studies (Reddy et al., 2011). The disadvantages of that treatment include depletion of B cells for up to six to nine months, no long-term cellular immune response to EBV, and poor effectiveness for central nervous system disease (Reddy et al., 2011).

Adoptive cellular therapy using T-cells to reconstitute anti-CMV immunity was first studied in 1995 (Walter et al., 1995). CTLs have been developed and used for CMV, adenovirus, and EBV infections. Virus-specific CTLs are generated in the laboratory using donor lymphocytes repeatedly stimulated with EBV-transformed B-cell lines, which contain antigen-presenting cells. Those cells can present viral antigens efficiently (Fujita, Rooney, & Heslop, 2008). Cellular therapy for EBV-associated PTLD is limited for cord blood transplantation recipients because of the lack of donor access and the donor’s naive neonatal immune system. Successfully treated cases have been reported for those patients using third-party EBV-specific CTLs (Barker et al., 2010); however, that treatment is not always successful because of tumor mutation resistance to CTL or poor specificity of CTL for EBV targets (Bollard et al., 2004). The other limitation of CTL therapy is the readiness of CTLs at the time of diagnosis of viral infection because the generation of EBV-specific CTLs requires two to three months (Bollard et al., 2004).

Discussion

Styczynski, Einsele, Gil, and Ljungman (2009) analyzed the outcome of current treatments for EBV-associated PTLD. Preemptive use of either a single administration of rituximab or one to four doses of EBV-specific CTLs (fixed or escalating doses) during a one-to-four-week time period significantly reduced the risk of death caused by PTLD in HCT recipients, with survival rates of about 90% and 94%, respectively (Styczynski, Einsele, et al., 2009). Ms. M’s EBV infection was not controlled with rituximab treatment. Trivirusspecific CTL initially seemed to control her adenovirus and EBV; however, she did not survive. Although Ms. M developed multiple complications, the rapid progression of PTLD was one of the major causes of her multiorgan failure.

The prognosis for EBV-associated PTLD is poor (Preiksaitis, 2010). CTL treatment has been promising for prophylaxis; however, it seems to be less successful in controlling PTLD in the later stage of the disease. As a result, prevention and early intervention in EBV infection are critical. Tomblyn et al. (2009) provided guidelines for preventing EBV complications among HCT recipients, including recommendations for avoiding exposure and disease (see Figure 2). All HCT donors or candidates should be tested for the presence of serum anti-EBV immunoglobulin G antibodies before transplantation to determine risk for primary EBV after HCT. The recommendation is stronger in pediatric patients than in adults (Tomblyn et al., 2009).

The most important measure for preventing EBV-related PTLD is to monitor EBV DNA load in patients at high risk (e.g., unrelated or mismatched transplantation, T-cell depletion, or antithymocyte globulin use). EBV DNA load has been shown to rise as early as three weeks prior to disease onset (Tomblyn et al., 2009). Monitoring blood EBV DNA load allows preemptive reduction in immunosuppression as the first part of patient management. If no response to the reduction in immunosuppression occurs, preemptive treatment with rituximab can prevent PTLD. Donor-derived EBV-specific CTL has demonstrated promise in the prophylaxis of EBV lymphoma in high-risk patients. In addition, expanded donor-derived EBV-specific T cells have been used experimentally to control EBV DNA loads. Finally, use of B-cell depletion of donor cells to minimize the risk of EBV PTLD also has been proposed (Tomblyn et al., 2009).

Implications for Nursing and Conclusions

HCT donors will undergo different types of blood tests per institutional standards and likely will be overwhelmed with information after the clinic visit. Nurses are positioned to educate HCT donors about the purpose of the tests and to ensure the required tests have been ordered correctly to prevent donors from having to make a second trip to the clinic. Nurses often are the first team members to know the test results, and they are responsible for ordering appropriate medications. In addition, nurses should follow up consistently on subsequent EBV DNA tests during and after treatment. Nurses are vital in EBV screening, infection recognition, disease prevention, and monitoring treatment response to help prevent or manage PTLD in transplantation recipients.

Preventing Exposure

➤ Test serum anti-EBV immunoglobulin G antibodies in all HCT donors. This recommendation particularly applies to pediatric patients.

Preventing Disease

➤ Assess EBV DNA load via quantitative polymerase chain reaction in high-risk patients.

➤ Immunosuppression reduction (e.g., steroid, tacrolimus or cyclosporine, mycophenolate, antithymocyte globulin) ➤ Initiate preemptive rituximab treatment.


EBV—Epstein-Barr virus; HCT—hematopoietic cell transplantation

FIGURE 2. Prevention of EBV Complications in HCT Recipients

Note. Based on information from Tomblyn et al., 2009.
References


