



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

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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.

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

Ms. 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 dys-

uria, 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/m<sup>2</sup>. 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