■ Article

Epstein-Barr Virus–Associated Post-Transplantation Lymphoproliferative Disorder:

Potential Treatments and Implications for Nursing Practice

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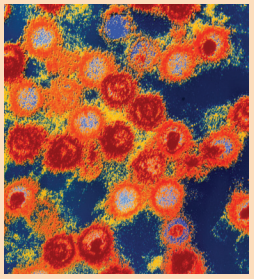

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Background: Considered to be a secondary malignancy, Epstein-Barr virus (EBV)–associated post-transplantation lymphoproliferative disorder (PTLD) is a potentially fatal complication of hematopoietic cell transplantation (HCT). With 50%–70% of all reported cases of PTLD being associated with EBV, the incidence in HCT is relatively low. However, mortality rates in this population of patients are 70%–90%.

Objectives: The focus of this article is to discuss published literature regarding the risk factors, clinical manifestations, diagnosis, prevention, and potential treatment options for EBV-PTLD, as well as nursing implications and the importance of patient education in high-risk HCT recipients.

Methods: This review of literature focused on locating, summarizing, and synthesizing data from published clinical studies that focused on treatment options, guidelines, and recommendations for EBV-PTLD. CINAHL® and PubMed databases were used to search for articles published within the past 10 years that included the following key words: *post-transplantation lymphoproliferative disorder*, *Epstein-Barr virus*, and *hematopoietic cell transplantation*.

Findings: Prevention and preemptive therapy are paramount when caring for patients undergoing HCT. Early determination of risk, close observation of EBV DNA levels in the blood, and prompt initiation of therapy are essential to improving patients' overall prognosis. Reduction in immunosuppression is considered first-line therapy for those diagnosed with EBV-PTLD. The literature also supports rituximab-based therapies, administration of EBV-specific cytotoxic T cells, and donor lymphocyte infusion as treatment strategies.

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One potentially life-threatening complication following solid organ transplantation and hematopoietic cell transplantation (HCT) is post-transplantation lymphoproliferative disorder (PTLD). The incidence of PTLD after HCT is relatively low (about 1%) (Al-Mansour, Nelson, & Evens, 2013). However, mortality rates in this population of patients are 70%–90% (Al-Mansour et al., 2013; Jagadeesh, Woda, Draper, & Evens, 2012; Zhong, 2012). About 50%–70% of PTLD cases are associated with Epstein-Barr virus (EBV), a common childhood virus that belongs to the family of herpes viruses and infects up to 95% of the American adult population (Jagadeesh et al., 2012; Zhong, 2012). Strategies for the prevention and treatment of PTLD remain a matter of debate; various approaches have been attempted to avoid the high morbidity and mortality associated with the diagnosis. Treatment may include manipulation of immunosuppressive therapies, surgery, radiation therapy, antiviral medications, chemotherapeutic agents, immunotherapy, or adoptive cellular therapies (Ahmad et al., 2009).

Post-Transplantation Lymphoproliferative Disorder Characteristics

EBV is associated with about 55%–65% of all PTLD cases (Al-Mansour et al., 2013). Latent EBV becomes a lifelong dormant

infection in B cells. In the setting of pharmacologic immunosuppression, uncontrolled B-cell proliferation is allowed because of decreased T-cell regulation and function. This uncontrolled proliferation of EBV-infected B cells gives rise to PTLD (Allen et al., 2002; Al-Mansour et al., 2013; Reshef et al., 2011). Studies have shown that cytotoxic T cell precursor frequencies are low at three months post-allogeneic HCT and normalize at 9–12 months, therefore correlating the period when EBV-PTLD is most frequent (Wingard, Gastineau, Leather, Snyder, & Szczepiorkowski, 2013). However, EBV-negative PTLD can occur (30%–45% of cases) and generally appears later (i.e., median of 62 months post-transplantation), carrying a worse prognosis than EBV-positive disease (Al-Mansour et al., 2013; Jagadeesh et al., 2012). The World Health Organization categorizes PTLD into four subtypes: early lesions, polymorphic, monomorphic, and classic Hodgkin lymphoma (Al-Mansour et al., 2013; Jagadeesh et al., 2012; National Comprehensive Cancer Network [NCCN], 2013; Swerdlow et al., 2008) (see Table 1). Early lesions, as well as polymorphic and monomorphic subtypes of PTLDs, are generally of B-cell origin, associated with T-cell dysfunction, and frequently derived from EBV, accounting for the majority of PTLD diagnoses (Wingard et al., 2013). However, T-cell PTLD has also been associated with poor prognosis (Zimmerman & Trappe, 2013).

Risk Factors

Several risk factors for developing PTLD exist for patients undergoing HCT. The primary risk factor contributing to PTLD in this population is the use of T-cell–depleted products (Ahmad et al., 2009; Al-Mansour et al., 2013; Jagadeesh et al., 2012). Other risk factors include human leukocyte antigen (HLA) mismatch; the use of umbilical cord cells, unrelated donor cells, antithymocyte globulin, and reduced-intensity conditioning regimens; haploidentical transplantations; an age of older than 50 years or younger than 10 years; the severity of graft-versus-host disease; transplantation for immunodeficiency disorders; and second transplantation (Ahmad et al., 2009; Al-Mansour et al., 2013; Jagadeesh et al., 2012; Weinstock, Ambrossi, Brennan, Kiehn, & Jakubowski, 2006; Yarbro, Wujcik, & Gobel, 2011; Zhong, 2012). Also contributing greatly to the risk of PTLD development is a primary infection of EBV with reactivation during immunosuppression, along with the use of EBV-seropositive donor cells in a previously seronegative recipient (Ahmad et al., 2009; Allen et al., 2002; Zhong, 2012). In HCT recipients, the majority of PTLDs are of donor origin. Therefore, EBV status is an important factor in donor selection (Jagadeesh et al., 2012).

Immunosuppression because of transplantation has been identified as a risk factor for those who have undergone HCT. The use of anti-CD3 antibodies, antithymocyte globulin, calcineurin inhibitors, cyclosporine, and tacrolimus as immunosuppressive agents has been implicated as a risk factor. However, the data are conflicting (Al-Mansour et al., 2013; Jagadeesh et al., 2012). Genetic susceptibility may be another potential risk factor for the development of PTLD. Host genetic variation is an emerging approach to predicting a patient's risk of PTLD. The polymorphisms of HLA loci and cytokine genes, such as interleukin-10 and interferon gamma, may lead to a predisposition to PTLD (Al-Mansour et al., 2013; Jagadeesh et al., 2012). However, further study is needed to validate the usefulness of this approach and to develop novel preventive strategies (Al-Mansour et al., 2013; Jagadeesh et al., 2012).

TABLE 1. World Health Organization Histologic Classifications of PTLD

Subtype	Clonal Status	EBV Status
Early Lesions • Plasmacytic hyperplasia • Infectious mononucleosis-like lesions	Polyclonal	Typically EBV positive
Polymorphic PTLD	Monoclonal	Typically EBV positive
Monomorphic PTLD • B-cell neoplasm – Burkitt lymphoma – Diffuse large B-cell lymphoma – Plasma cell myeloma – Plasmacytoma-like lesion • T/NK-cell neoplasm – Hepatosplenic T-cell lymphoma – Peripheral T-cell lymphoma not otherwise specified	Monoclonal	Frequently EBV positive Rarely EBV positive
Classic Hodgkin lymphoma–like PTLD	Monoclonal	Frequently EBV positive

EBV—Epstein-Barr virus; NK—natural killer; PTLD—post-transplantation lymphoproliferative disorder

Note. Based on information from Swerdlow et al., 2008.

Clinical Presentation and Diagnosis

In HCT recipients, the clinical presentation of PTLD often has a rapid onset (i.e., four to six months after HCT), is more aggressive in nature than it is following solid organ transplantation, and presents as widely disseminated disease with multiorgan involvement (Al-Mansour et al., 2013; Jagadeesh et al., 2012). Common presenting symptoms include anorexia, fatigue, fever, lymphadenopathy, multiorgan failure, sepsis-like syndrome, and weight loss. Extranodal involvement most frequently affects the gastrointestinal tract, but also commonly involves the bone marrow, central nervous system, lungs, and skin (Al-Mansour et al., 2013; Jagadeesh et al., 2012; Weinstock et al., 2006).

Given the aggressive nature of PTLD, early diagnosis and prompt treatment are essential to a patient's overall prognosis. The standard testing to confirm a diagnosis of PTLD includes histopathology, immunophenotyping of tissue samples, and immunohistochemical evaluation, as well as EBV testing to determine whether the virus is a primary infection or a reinfection (NCCN, 2013). Further diagnostic testing should include an evaluation of performance status, as well as a complete blood count with differential and a metabolic panel that includes albumin, electrolytes, blood urea nitrogen, and creatinine, along with lactate dehydrogenase (LDH) measurements. A review of

Pre-Transplantation Education and Monitoring

Establish Epstein-Barr virus (EBV) status of recipient and donor by testing for the presence of EBV antibodies.

- Patient and donor notification of EBV status

Provide education regarding risk of developing EBV-associated post-transplantation lymphoproliferative disorder (PTLD).

- Conditioning regimen used
  - Reduced-intensity conditioning regimens
- Disease being treated by transplantation
  - Immunodeficiency disorders
- EBV status of recipient and donor, as well as personal history of EBV
- Planned immunosuppressive therapy
  - Anti-CD3 antibodies
  - Antithymocyte globulin
  - Calcineurin inhibitors
  - Cyclosporine
  - Tacrolimus
- Recipient age
  - Older than 50 years or younger than 10 years
- Severity of graft-versus-host disease
- Type of transplantation, match grade, graft source
  - Haploidentical transplantation
  - Human leukocyte antigen mismatched donor
  - Second transplantation
  - T-cell–depleted products
  - Umbilical cord transplantation
  - Unrelated donor

Provide education regarding symptoms of PTLD.

- Anorexia or weight loss
- Fatigue
- Fever
- Lymphadenopathy
- Multiorgan failure
- Sepsis-like syndrome

Provide information regarding prevention and preemptive treatment.

- Weekly quantitative testing of EBV DNA
- Possible preemptive treatments
  - Infusion of cytotoxic T cells
  - Infusion of unmanipulated donor leukocytes
  - Reduction in immunosuppression
  - Rituximab

Post-Transplantation Education and Monitoring

Reinforce education related to weekly quantitative testing of EBV DNA.

- Consider preemptive therapy if increase in EBV DNA levels is found.

Closely monitor reported symptoms and test results in high-risk patients.

Emphasize education regarding symptoms of PTLD and the time frame during which they typically arise (i.e., six months after transplantation).

Provide and reinforce education related to potential treatments, including side effects, toxicities, and risk of infection.

FIGURE 1. Guidelines for Pre- and Post-Transplantation Patient Education and Monitoring

the patient's history of immunosuppressive therapy should also take place, as should Hepatitis B virus testing and computed tomography scans of the chest, abdomen, and pelvis (NCCN, 2013). In certain cases, bone marrow biopsy, positron-emission tomography, lumbar puncture, and magnetic resonance imaging of the brain may be ordered, depending on presentation of symptoms (NCCN, 2013).

Management

Reduction in Immunosuppression

Reduction in immunosuppression is considered to be a first-line therapy (NCCN, 2013); it allows recovery of the physiologic immune surveillance of EBV-transformed B cells and regulation of T-cell function (Reshef et al., 2011). In a retrospective analysis of 67 transplantation recipients with PTLD, the use of reduction of immunosuppression as initial therapy was shown to have high response rates (23 patients achieved complete response and 5 achieved partial response), leading to a favorable outcome. In another retrospective study, predictors of poor response included bulky disease, advanced disease stage, and older age. For participants with low-risk disease who were treated with reduction in immunosuppression alone, the survival rate was 44 months, compared to 9.5 months for those who remained on full immunosuppression (Reshef et al., 2011). However, in a separate prospective multicenter phase II trial, 16 patients were treated with reduction in immunosuppression. No participants achieved complete response, but one participant achieved partial response. Six of the 16 participants had documented rejection, and progressive disease was noted in 8 of 16 participants (Swinnen et al., 2008).

Rituximab-Based Therapy

The efficacy and safety of rituximab-based therapy is well documented in phase II trials. In a prospective multicenter phase II trial, 43 participants were treated with four weekly infusions of rituximab 375 mg/m^2 (Choquet et al., 2006). At day 80, 37 patients were alive, with a response rate of 44%. At day 360, the response rate was 68%. The one-year survival rate was 67%. The only predictor of response in this study was a normal LDH level (Choquet et al., 2006).

Coppoletta et al. (2011) found that of 55 patients who tested positive for the presence of more than 1,000 EBV copies/10^5 peripheral blood mononuclear cells (PBMCs), 50 cleared EBV after one to four doses of rituximab. In this study, factors predicting transplantation-related mortality were a reduction to less than 1,000 EBV copies/10^5 PBMCs by day +7 and disease status in remission (first complete remission or second complete remission [CR2]). Transplantation-related mortality was higher in patients with disease statuses beyond CR2. The overall five-year survival rate was 32%, with a 40% five-year survival rate for patients with zero or one negative predictive factors and 13% for those with both negative predictors (Coppoletta et al., 2011).

In an international prospective multicenter phase II trial, Trappe et al. (2012) investigated sequential treatment with rituximab followed by cyclophosphamide, hydroxyl doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. Patients with a complete response following four doses of rituximab 375 mg/m^2 received a four-week break and then underwent four cycles of CHOP chemotherapy, each cycle being administered every three weeks. If any signs of clinical progression were evident during rituximab monotherapy or during the break period, patients proceeded to CHOP chemotherapy. Overall, 60% of patients had either a complete response or a partial response following rituximab monotherapy, then a 90% complete response following sequential CHOP chemotherapy. The median overall

survival rate was 6.6 years, and the median progression-free survival rate was four years (Trappe et al., 2012). These studies support the initiation of early rituximab-based therapy to improve survival outcomes.

Adoptive Immunotherapy

Although considered to be a second-line therapy, infusions of EBV-specific cytotoxic T cells have been used to prevent and treat PTLD in patients who have undergone HCT (Jagadeesh et al., 2012; NCCN, 2013). Rooney et al. (1998) found that of the 39 pediatric patients who were deemed at high risk for developing PTLD and who were administered two to four infusions of donor-derived EBV-specific cytotoxic T cells following T-cell–depleted bone marrow transplantations, none developed EBV-PTLD, compared to about 12% of patients in the control group. Infusions of cytotoxic T cells also were effective in reducing EBV DNA levels in the blood of patients. In addition, two patients with diagnosed PTLD were effectively treated. No cases of graft-versus-host disease caused by the infusion were reported, and 27 patients on the prophylactic arm remained alive 15–54 months after transplantation (Rooney et al., 1998). A phase II multicenter trial of 33 transplantation recipients with EBV-PTLD revealed that 21 patients had either a complete response or a partial response at five weeks following the infusion of third-party allogeneic EBV-specific T cells. The overall response rate was 52% at six months, and the overall survival rate was 79% at six months. At five weeks, the patients receiving infusions with a higher percentage of CD4-positive cells had a better response. Patients receiving cytotoxic T cells with closer HLA matching also responded better than those receiving cytotoxic T cells with fewer matches (Haque et al., 2007).

Antiviral Therapy

The use of antiviral therapies to prevent PTLD is not recommended because of a lack of conclusive evidence to support such treatment (Tomblyn et al., 2009). In a case-controlled study, antiviral prophylaxis was associated with a 44% reduction in early PTLD risk as compared to those who received no antiviral coverage. Stronger benefit was shown during the first year following transplantation; a 38% reduction in risk occurred with the use of gancyclovir. Neither acyclovir nor gancyclovir demonstrated a protective effect on late PTLD (Funch, Walker, Schneider, Ziyadeh, & Pescovitz, 2005). Additional randomized, controlled studies are needed to confirm the validity of antiviral therapies to either prevent or treat EBV infection. In vivo, both antivirals are ineffective against EBV because they do not eradicate latent EBV in the infected B cells (Allen et al., 2002; Al-Mansour et al., 2013; Jagadeesh et al., 2012; Tomblyn et al., 2009).

Prevention and Preemptive Therapy

The most important measure prior to transplantation, which aids in the prevention and early determination of risk, is serological testing for antibodies specific for EBV antigens of the recipient and prospective donors. In addition, recipients who are deemed high risk (e.g., T-cell–depleted products, use of antithymocyte globulin, mismatched donor transplantation, umbilical cord transplantation, haploidentical transplantation) should be closely monitored, with weekly testing to quantify the amount of EBV DNA in the blood (Tomblyn et al., 2009). Because of differences in polymerase chain reaction techniques, no firm recommendations exist regarding the threshold for initiation of preemptive therapy (Tomblyn et al., 2009).

Primary goals in the preemptive treatment of PTLD are disease control and preservation of allograft function. Close monitoring of EBV DNA can allow for preemptive reduction in immunosuppression as first-line management; Epstein-Barr viremia has been shown to rise as early as three weeks prior to disease onset (NCCN, 2013; Tomblyn et al., 2009). If immunosuppressant reduction does not produce a response, preemptive treatment with rituximab can prevent PTLD (NCCN, 2013; Tomblyn et al., 2009). In addition, various strategies, such as infusions of donor-derived, EBV-specific cytotoxic T cells and unmanipulated donor lymphocyte infusions, have shown promising results in the prophylaxis of EBV-PTLD in recipients of T-cell–depleted unrelated or mismatched allogeneic recipients (Tomblyn et al., 2009).

Implications for Practice

- Provide recipients and caregivers with education regarding risk factors and symptoms of Epstein-Barr virus (EBV)–associated post-transplantation lymphoproliferative disorder (PTLD).
- Inform recipients about the importance of EBV DNA monitoring and potential preemptive treatments.
- Regularly assess recipients for EBV-PTLD signs and symptoms.

Implications for Nursing

Nurses have the ability to provide valuable information during the transplantation recipients' journey. Therefore, nurses should educate HCT candidates about the side effects and complications associated with HCT. This information should be reinforced throughout patients' hospitalization and outpatient clinic visits. In addition, education should be provided regarding the testing required to establish EBV status of the donor and recipient, as well as the rationale behind the serial testing needed to monitor EBV status in the post-transplantation period (see Figure 1).

Prompt communication of test results to the physician is equally important; nurses are usually the first to be notified of abnormal values. Timely communication can result in rapid initiation of therapy based on quantitative levels of EBV DNA. Various treatments, including rituximab-based therapy and CHOP chemotherapy, are administered by nurses who again provide patients with information regarding the medication or infusion and its potential side effects and reactions. They also are responsible for monitoring toxicities and instructing patients about the risk of infection. Nurses play a vital role in education, screening, recognition of infection and symptoms of PTLD, prevention of disease, and monitoring of prescribed treatment response, all of which help to ensure successful transplantation recovery.

Conclusion

EBV-PTLD is a potentially fatal complication of HCT that has a relatively high mortality rate. Prevention and preemptive therapy are imperative. Factors that contribute to risk should be assessed prior to transplantation, and serial monitoring of EBV DNA in the blood should be implemented in those found to be at high risk of infection or disease reactivation. Nurses should be aware of the importance of serial monitoring and promptly report test results to the transplantation physician to facilitate preemptive treatment. In addition, nurses are instrumental in providing education to transplantation recipients, as well as in performing ongoing nursing assessments; both are crucial to ensuring the best possible management and overall outcome.

Reduction in immunosuppression as a first-line therapy has been well documented. Other strategies include rituximab-based therapies, administration of EBV-specific cytotoxic T cells, and donor lymphocyte infusion. Further randomized, controlled trials are needed to support the use of antivirals. Additional research is necessary to explore host variations in polymorphisms of HLA loci and cytokine genes, which may reveal a predisposition to PTLD and lead to individualized preventive strategies.

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