Post-transplant Lymphoproliferative Disorders

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INTRODUCTION

There is an increased risk of malignancy after both solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT). In patients who undergo SOT, the second most common malignancy after nonmelanoma skin cancers is post-transplant lymphoproliferative disorders (PTLD). The term PTLD includes disorders ranging from benign hyperplasia to malignant lymphomas occurring in the setting of immunosuppression during SOT and HCT. The first cases of PTLD were described in renal transplant recipients in the late 1960s. Since then, PTLD has remained a serious and sometimes fatal complication in the post-transplant setting.

EPIDEMIOLOGY

PTLD is the most common malignancy in children who undergo SOT. Primary Epstein-Barr virus (EBV) infection after transplantation is the cause of this high incidence. In adults, PTLD is seen in up to 10% of all SOT recipients. However, different types of transplants result in varying degrees of risk of PTLD; this is thought to reflect the characteristics of both the specific tissue type and the immunosuppressive regimen used in different transplants. The incidence of PTLD is highest after small bowel transplantation (20%), followed by lung (10%), heart (6%), and liver transplants (2.8%). The incidence of PTLD is lowest in renal transplant recipients (2.3%). Historically, the incidence of PTLD has been highest during the first year post-transplant. A collaborative transplant study reported a PTLD incidence of 224 per 100,000 in the first year post-transplant, 54 per 100,000 in the second year, and 31 per 100,000 in the sixth year. This study also demonstrated that the incidence of PTLD during the first year after transplant was higher in combined heart-lung and lung recipients, which was attributed to more aggressive immunosuppression within the first year. However, more recent series show a median time to PTLD onset after SOT of 30 to 40 months.

PTLD is comparatively less common after allogeneic HCT, although it is still a potentially fatal complication in this setting. In large retrospective studies, PTLD occurred in 0.5% to 2.5% of patients after HCT, with the peak incidence occurring between 2 and 6 months post-transplant. Nearly all cases of early-onset PTLD after HCT are associated with EBV infection. Late-onset PTLD following HCT can also occur, with some cases being EBV-negative or of T-cell origin in this setting.

CLASSIFICATION AND PATHOLOGY

The classification of PTLD is based on the histopathologic appearance of the tumor and is categorized according to the 2008 World Health Organization (WHO) classification. The 4 WHO categories of PTLD are early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma. In the United States and Europe, most PTLD lesions (>85%) are of B cell origin, and more than 80% of these are EBV-positive. Early lesions maintain normal tissue architecture and present with 2 histological patterns—plasmacytic hyperplasia and an infectious mononucleosis–like form. Polymorphic PTLD is composed of a combination of lymphoid cells including small- to medium-sized lymphocytes, immunoblasts, and mature plasma cells with degradation of the underlying architecture. Polymorphic lesions may be either polyclonal or monoclonal but do not meet the diagnostic criteria for B-cell or T/NK cell lymphoma.

The most common form of PTLD is monomorphic PTLD. Monomorphic lesions include monoclonal lymphoid proliferations and are divided into B-cell PTLD and T-cell PTLD. Monomorphic B-cell PTLDs include diffuse large B-cell lymphoma (DLBCL), the largest category of monomorphic lesions, followed by Burkitt lymphoma. Monomorphic B-cell PTLD also includes plasma cell myeloma and plasmacytoma–like lesions. Monomorphic T-cell PTLD, including T/NK
cell lesions, is rare and occurs in approximately 15% of PTLD. The majority of T-cell lesions are EBV-negative, whereas the majority of NK lesions are EBV-positive. T-cell PTLDs are further divided into peripheral T-cell lymphomas and rare types such as gamma-delta T-cell lymphomas and hepatosplenic T-cell lymphomas. T-cell PTLD usually occurs later and carries a poorer prognosis than B-cell PTLD. Though there may not be an association with EBV infection, there is an increasing incidence of T-cell lymphomas in Japan due to the higher prevalence of human T-lymphotropic virus type 1 (HTLV-1). Classical Hodgkin lymphoma–type PTLD is rare and is usually found as a late complication post-transplant.

**RISK FACTORS FOR DEVELOPMENT OF PTLD**

**AFTER SOLID ORGAN TRANSPLANTATION**

There are many risk factors that contribute to the development of PTLD after SOT. The factor which strikingly elevates the risk of developing PTLD is primary EBV infection occurring after transplantation when an EBV-seronegative recipient receives an allograft from an EBV-seropositive donor. Several single-center analyses have demonstrated a 10- to 76-fold greater incidence of PTLD in EBV-seronegative recipients. The link between an EBV-seronegative recipient and PTLD development was first recognized in 1985. This is more of a concern in pediatric transplant recipients because over 90% of the adult population already has immunity to EBV. Other risk factors include the amount and duration of immunosuppression along with transplant type. The type of SOT not only determines the amount of immunosuppression, but also carries specific biologic characteristics which may contribute to risk. For example, in lung transplants bronchus-associated lymphoid tissue can carry EBV-infected donor lymphocytes. Late-onset PTLD is associated with several risk factors, including EBV-negative status, older recipient age, and the duration rather than the type of immunosuppression.

Individual immunosuppressants are also risk factors for PTLD. These include tacrolimus and cyclosporine, which are the backbone of most immunosuppressive regimens. Their use initially was associated with an increased incidence of PTLD, but using lower doses appears to decrease this risk. The use of antilymphocyte antibodies for prophylaxis or treatment of acute rejection is also implicated as a risk factor. These include T-cell depleting antibodies such as OKT3, which is a monoclonal antibody against CD3, and antithymocyte globulin (ATG). OKT3 not only disables the function of cytotoxic T cells, but also heightens cytokine activity, allowing amplification of EBV-infected B cells. Analysis of the Collaborative Transplant Study database of approximately 200,000 patients demonstrated that use of either OKT3 or ATG was associated with a 3- to 4-fold increased risk of PTLD. It appears that the combined effect of immunosuppression rather than any one agent determines the incidence of early-onset PTLD.

Infection with hepatitis C virus and human herpesvirus-8 (HHV-8) post-transplant may also increase the risk of PTLD. Age younger than 10 years or older than 60 years has also been associated with increased risk of PTLD. For patients over 60 years of age, the increased incidence of PTLD may be associated with less efficient immune surveillance of EBV-infected lymphocytes. If risk factors are combined (pretransplant EBV seronegativity, cytomegalovirus mismatch, and OKT3 exposure), they have a synergistic effect contributing to a 500-fold increased risk of PTLD after SOT, compared to those without any of these factors.

**AFTER HEMATOPOIETIC CELL TRANSPLANTATION**

The primary factor contributing to the development of PTLD after allogeneic HCT is T-cell depletion of the donor hematopoietic marrow or peripheral blood stem cell product. Those patients undergoing myeloablative conditioning regimens with administration of T-cell depleting antibodies have a higher risk of developing EBV-associated PTLD, since development of the EBV-specific cytotoxic T-cell response in the marrow recipient is delayed. T-cell–depleting agents which selectively target T-cell and/or T/NK cell populations are associated with a higher risk of PTLD than those that deplete both T and B cells such as alemtuzumab. The degree of HLA-mismatching also predisposes to PTLD, with a 4.3-fold increased risk of PTLD documented in those with an HLA mismatched donor. An international multicenter study of more than 25,000 patients identified additional predisposing factors for PTLD after allogeneic HCT, including the presence and/or severity of graft-versus-host disease (GVHD) and age older than 50 years at the time of transplantation. Similar to SOT, EBV serology remains a risk factor for PTLD development in HCT. Specifically, the combination of an EBV-seronegative recipient and an EBV-seropositive donor strongly increases PTLD risk. Post-HCT PTLD may still occur in EBV-seropositive recipients with a seropositive donor, but it is very rare for PTLD to occur after HCT when an EBV-seronegative donor is utilized. Cytomegalovirus seropositivity in
either the donor or recipient may also increase the risk of PTLD after HCT.8

When multiple risk factors are combined, patients at particularly high risk for PTLD after HCT can be identified. For example, using 4 risk factors (T-cell depletion using selective T-cell depletion methods, use of ATG to prevent or treat acute GVHD, use of an HLA-mismatched donor in association with selective T-cell depletion or ATG therapy, and age >50 years at transplant), the cumulative risk of PTLD at 12 years ranged from 0.2% to 8.1%.9 Another study identified 3 risk factors for PTLD development: HLA mismatch, EBV serology mismatch, and splenectomy. The incidence of PTLD was 0.26% for patients with none of these risk factors, 8.2% for those with 1 risk factor, and 35.7% for those with 2 risk factors; in this study, the overall rate of PTLD was 2.5%.8

**PATHOGENESIS**

After SOT the majority of PTLD cases are of recipient origin, whereas after HCT the majority of PTLD cases are of donor origin.14 As described above, in many cases EBV is intricately involved with the pathogenesis of PTLD (Figure). The majority of PTLD lesions arise from either primary EBV infection or from EBV reactivation, since most adults are already EBV-seropositive at the time of transplantation.38–40 EBV is a gamma-herpesvirus acquired by over 90% of the world’s population by adolescence.41 EBV persists throughout the host’s lifetime.50 During primary infection, EBV infects B lymphocytes by interacting with the B-cell EBV receptor CD21. EBV-infected B cells proliferate and express EBV-encoded proteins, and of these proteins Epstein-Barr nuclear antigen (EBNA) and latent membrane protein (LMP) are the most important.3 The expression of EBV-encoded proteins leads to a primary cytotoxic T-cell response. However, EBV-infected B cells are not completely eliminated by this initial cytotoxic T-cell response. LMP1, which prevents apoptotic signaling, then drives infected cells into a latent phase.5 These memory cells downregulate EBV-encoded proteins, but there remains enough expression to promote a secondary cytotoxic T-cell response. The ongoing proliferation balances the destruction of EBV-infected B cells and EBV persists as a subclinical infection. With immunosuppression, the balance is shifted towards B-cell proliferation, leading to EBV-driven lymphoproliferation.42

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**Figure.** Pathophysiology of Epstein-Barr virus (EBV)-positive post-transplant lymphoproliferative disorder (PTLD). EBV enters B lymphocytes through interaction with the EBV receptor CD21. EBV-infected B cells then undergo proliferation and express viral latency genes, including Epstein-Barr nuclear antigens (EBNA) and latent membrane protein (LMP). This leads to a primary EBV-restricted cytotoxic T-cell (CTL) response, which is only partly effective. The EBV-infected B cells are then able to establish a persistent infection (latency) in memory B cells. These memory B cells have a more limited expression of viral antigens, which leads to a secondary CTL response. These secondary CTLs counteract the ongoing proliferation of the memory B cells, and a balance is established. Immunosuppression perturbs this balance, which can then lead to uncontrolled EBV-driven proliferation and PTLD.
immunosuppression, some of these B cells undergo a selective proliferation advantage by acquiring bcl-6 mutations,\(^\text{45}\) \(c-myc\) rearrangements, or p53 tumor suppressor gene disruptions.\(^\text{3,44–46}\) This transitions polyclonal proliferations into oligoclonal or monoclonal proliferations.\(^\text{30}\) Though the majority of transplant recipients are EBV-seropositive and receive immunosuppression, only a minority develop PTLD. It is therefore thought that other stimuli must be involved in the pathogenesis of EBV-driven lymphoproliferation.\(^\text{3}\) Additional stimuli may include chronic B-cell stimulation by alloantigen and cytokines. For example, tumor biopsies have demonstrated a CD4 T-cell infiltrate and increased levels of interleukin (IL)-4, IL-6, and IL-10 along with interferon (IFN)-\(\alpha\).\(^\text{47–50}\) Decreased expression of IFN-\(\alpha\) may also contribute to PTLD.\(^\text{30}\)

Not all cases of PTLD result from EBV-driven lymphoproliferation.\(^\text{3}\) EBV-negative PTLD is increasingly recognized as a separate entity from EBV-positive PTLD. There appears to be an increasing incidence of EBV-negative PTLD, which has been attributed to changing immunosuppressive regimens, improved diagnostic techniques for PTLD, implementation of “preemptive” early therapy of PTLD with rituximab, and longer overall survival of patients post-transplant.\(^\text{41,52}\) EBV-negative PTLD occurs later, with a median time of 50 to 60 months post-transplant, has more aggressive features, and is more commonly of the monomorphic subtype.\(^\text{52,53}\) The pathogenesis of EBV-negative PTLD remains uncertain. The dynamic among genetic aberrancy, viral oncogenicity, immunosuppression, and chronic antigen stimulation underlies both EBV-negative and EBV-positive PTLD, leading to a variety of lymphoproliferative disorders.\(^\text{41}\)

**DIAGNOSIS AND STAGING**

The gold standard for diagnosing PTLD is pathologic examination of tissue after an excisional biopsy. In cases where PTLD involving an allografted organ is suspected, a fine-needle aspirate may be the only feasible biopsy option.\(^\text{31}\) In addition to pathologic evidence of monoclonality or oligoclonality, demonstration of disruption of underlying tissue architecture by a lymphoproliferative process and evidence of EBV infection are important factors in establishing a diagnosis of PTLD.

Available assays relating to EBV infection include EBV serology, viral load determination, or detection of EBV nucleic acids or proteins within tissue.\(^\text{32}\) The gold standard for diagnosing EBV-positive PTLD is in situ hybridization targeting EBV-encoded small nuclear RNA (EBER).\(^\text{34,55}\) EBER expression occurs in all types of EBV latency.\(^\text{56}\) EBV-latent antigens in tissue may also be detected by immunohistochemistry using antibodies against EBNA-1, EBNA-2, and LMP1.\(^\text{55}\) Serologic testing, including EBV antiviral capsid antigen IgM and IgG antibodies, anti-early antigen, and anti-EBNA, is ubiquitous, but it is unreliable in immunosuppressed patients due to either delayed or absent humoral responses.\(^\text{29,41}\) EBV viral load is also used for diagnosis since an elevated viral load quantified by EBV-DNA polymerase chain reaction (PCR) is an established risk factor for EBV-related PTLD.\(^\text{57,58}\) Some centers routinely follow viral load in transplant recipients and preemptively treat those with a positive EBV PCR. This practice may decrease the frequency of overt EBV-related PTLD.\(^\text{59}\) There is no consensus on the frequency of testing but rather this is dependent on existing institutional protocols. The limitations of viral load monitoring are the lack of an international standard reference and reporting units.\(^\text{60}\)

A baseline work-up includes laboratory tests such as a complete blood count, differential, comprehensive metabolic panel, uric acid, lactate dehydrogenase, and HIV and hepatitis serologies. A lumbar puncture is recommended if central nervous system (CNS) involvement is suspected. Pretreatment assessment should also include a staging computed tomography scan of the neck, chest, abdomen, and pelvis and/or a positron emission tomography scan. Bone marrow biopsy is performed in some cases, particularly if cytopenias are present.\(^\text{15}\) There is no staging system which fully encompasses the spectrum of PTLD; however, at present the Ann Arbor staging classification system is used.

**CLINICAL MANIFESTATIONS**

The clinical presentation of PTLD varies depending on the location and degree of organ involvement. Symptoms may include lymphadenopathy, weight loss, fatigue, and fever. HCT recipients may present with fulminant PTLD with disseminated systemic disease clinically resembling septic shock.\(^\text{61}\) The classic presentation of diffuse lymphadenopathy is less commonly seen with PTLD as compared with lymphoma in the nontransplant setting.\(^\text{52}\) Extranodal involvement is common and may include the gastrointestinal tract, lung, kidney, skin, bone marrow, and CNS.\(^\text{6,52,63,64}\) The gastrointestinal tract is the most commonly affected extranodal site (22%–25%).\(^\text{63,65}\) CNS involvement occurs in 10% to 20% of cases,\(^\text{66–68}\) with kidney recipients having the highest incidence.\(^\text{66,69}\) Allograft involvement may occur
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in 30% of patients and is especially common after lung transplantation.\(^5\)

**Prognosis**

A number of variables have been associated with overall survival for PTLD. In a recent French registry study of 500 patients with PTLD after kidney transplantation, factors associated with inferior survival were age greater than 55 years at diagnosis, serum creatinine greater than 133 µmol/L, elevated lactate dehydrogenase (LDH), disseminated PTLD, CNS PTLD, T-cell PTLD, monomorphic PTLD, and serous membrane invasion. A 5-point prognostic score was constructed using the following variables: age greater than 55 years, serum creatinine greater than 133 µmol/L, elevated LDH, disseminated PTLD, and monomorphic histology. Patients were classified as low risk (score of 0), moderate risk (score of 1), high risk (score of 2–3), and very high risk (score of 4–5). Five-year overall survival was 92%, 83%, 59%, and 25%, respectively.\(^7\)

A large retrospective observational study from the University of Michigan of patients undergoing SOT between 1964 and 2007 identified 78 patients with PTLD. In this study, Ann Arbor stage III or IV, CNS involvement, and international prognostic index (IPI) scores of 3 to 5 were associated with a significantly higher risk of death.\(^6\)

In a recent study of 97 patients with PTLD after SOT who were managed with reduction in immunosuppression alone or surgical resection followed by reduction of immunosuppression, predictors of poor survival were age greater than 50 years, presence of B symptoms, bone marrow and liver involvement, HCV infection, an elevated LDH, and dyspnea.\(^7\)

Over the past decade, a new treatment paradigm for incorporating rituximab into first-line treatment has evolved. Several recent analyses have reexamined PTLD prognosis in the rituximab era. A multicenter analysis of 80 patients who developed PTLD after SOT found 3 factors predictive of progression and survival: CNS involvement, bone marrow involvement, and hypoalbuminemia. Using these 3 factors (0, 1, or 2–3), 3-year survival was 93%, 68%, and 11%, respectively.\(^7\)

A recent analysis of 60 post-SOT PTLD patients treated with rituximab identified 3 risk factors predictive of survival: age ≥60 years, ECOG performance status ≥2, and an elevated LDH. Patients with 0, 1, or 2 or 3 factors had a 1-year survival of 100%, 79%, and 36%, respectively, and a 2-year survival of 88%, 50%, and 0%, respectively.\(^7\)

Though CNS disease is associated with poor prognosis, improved outcome with rituximab and/or high-dose methotrexate has been demonstrated.\(^15\)

**Treatment**

**Reduction of immunosuppression**

The goal of treatment is cure of the PTLD along with preservation of graft function.\(^14\) However, there is no unifying consensus on the approach to treating PTLD due to a paucity of prospective phase II studies and few, if any, randomized phase III trials.\(^10,27\) Rather, the initial management is dependent on the specific clinical scenario and PTLD type. Treatment may involve reduction of immunosuppression (RIS), rituximab, chemotherapy, radiation therapy, surgery, or a combination of these strategies (Table).\(^74\)–\(^80\)

The treatment paradigm for PTLD generally calls for RIS as the initial intervention.\(^81\) Implementation of RIS theoretically allows partial restoration of host cytotoxic T-cell function, resulting in elimination of infected lymphocytes.\(^3\)

The morphologic classification of PTLD may determine response to RIS. Those patients more likely to respond to RIS include those with early lesions and polyclonal PTLD. Monoclonal tumors, especially those with bel-6 expression, are usually unresponsive to RIS as the sole treatment.\(^92,83\) EBV-positive PTLD is also more likely to respond to RIS.\(^84\)

There are, however, several potential problems that can arise with RIS. One concern is the risk of graft rejection and organ failure. Dose reduction is dependent upon the extent of disease and whether the patient has a life-sustaining graft such as a heart transplant. As an example, the dose of cyclosporine or tacrolimus may be reduced over 4 to 6 weeks to achieve trough levels of around 25% to 50% of the levels that were observed in the patient leading up to the diagnosis of PTLD. Many clinicians recommend a 50% reduction in immunosuppression unless this is felt to pose an unacceptably high risk of graft rejection. In addition, antiproliferative agents such as azathioprine or mycophenolate should be dose-reduced or discontinued.\(^3\)

A second concern with RIS is the long time to response, since early lesions may take 3 to 5 weeks or longer to improve. Those with multi-organ involvement often require more intensive upfront treatment to facilitate a more rapid clinical response. The third concern is that RIS is often inadequate as the sole treatment modality for aggressive disease. Using RIS as the sole treatment modality is associated with complete remission rates of 0 to 50%.\(^56,85\)–\(^88\) A recent study identified patients who would not achieve complete remission...
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Those patients with an elevated LDH level and multi-organ involvement were less likely to respond to RIS. However, in a separate study, age younger than 50 years, nonbulky disease (mass <7cm), and localized disease (Ann Arbor stage 1–2) predicted a higher chance to respond to RIS alone. Studies have also examined factors predicting response to rituximab. For example, a recent analysis developed a risk score for identifying patients likely to respond to the combination of RIS and rituximab monotherapy. In one study, the 2 factors predictive of progression-free survival were an elevated LDH and time to development of PTLD after transplantation. The factors that were predictive of poor overall survival were age greater than 60 years, impaired performance status, and elevated LDH. Given these results, a strategy that includes upfront RIS, rituximab, and chemotherapy may be beneficial for such “high-risk” patients.

RITUXIMAB

Rituximab is a chimeric monoclonal antibody targeted at the B-cell receptor CD20, which is expressed on both mature and immature B lymphocytes. Rituximab is generally very well tolerated with low toxicity; however, there is limited long-term experience with PTLD. Furthermore, exactly when rituximab should be introduced in the treatment algorithm is a matter of debate. Most studies have examined rituximab for patients who have failed to respond to RIS. However, a recent multicenter retrospective analysis demonstrated a benefit in using rituximab earlier in the treatment course. There was significantly improved progression-free survival and overall survival with initial concurrent rituximab and RIS. Several nonrandomized phase II clinical trials have employed rituximab for post-SOT PTLD, generally after failure of RIS. In these studies, an overall response rate of 44% to 66% has been observed, with a median survival between 14 and 42 months documented (Table).

Table. Results of Prospective Phase II Clinical Trials in Post–Solid Organ Transplant PTLD

<table>
<thead>
<tr>
<th>N</th>
<th>EBV Association, %</th>
<th>Treatment: Upfront</th>
<th>Treatment</th>
<th>ORR,% (95% CI)</th>
<th>Median OS (mo)</th>
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<td>Choquet et al76</td>
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<td>Rituximab + CP</td>
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<td>100a</td>
<td>RIS</td>
<td>Allogeneic EBV-specific cytotoxic T cells</td>
<td>64 (47–78)</td>
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</table>

*aInclusion criteria for study.
†Median OS not yet reached.

CHOP = cyclophosphamide (750 mg/m²) on day 1, doxorubicin (50 mg/m²) on day 1, vincristine (1.4 mg/m²) on day 1, prednisone (50 mg/m²) on days 1–5, with a 21-day cycle for a total of 2 cycles; CP = low-dose cyclophosphamide + prednisone; EBV = Epstein-Barr virus; ORR = overall response rate; OS = overall survival; RIS = reduced immunosuppression.
monotherapy.\textsuperscript{15} Although CHOP is the most widely used chemotherapy, such anthracycline-containing regimens should be used cautiously in heart transplant patients. In situations where a rapid clinical response is desired (such as those with organ compromise or high-grade lymphoma), chemotherapy is often employed as part of initial treatment. A retrospective analysis in which CHOP was used as initial treatment along with RIS in monomorphic PTLD patients demonstrated a complete response rate of 69\% and a 5-year disease-free survival of 62\%.\textsuperscript{92} The authors concluded that patients with morphologically high-grade PTLD should receive initial treatment with chemotherapy. In cases with highly aggressive histology (such as Burkitt lymphoma), chemotherapy is recommended as part of the initial therapy. However, in patients who are status post renal transplant, standard Burkitt lymphoma regimens (such as the hyper-CVAD or Magrath regimens) may not be feasible because these regimens incorporate high doses of alkylating agents and high-dose methotrexate, which pose a significant risk of toxicity in transplant patients (particularly patients with kidney transplants). In such cases, alternative regimens (such as R-CHOP or R-EPOCH) may be preferred, although it should be emphasized that there is no standard regimen for Burkitt PTLD.\textsuperscript{93}

Many clinicians utilize a “staged” approach to PTLD therapy, in which RIS ± rituximab is employed first. Those who do not achieve remission with this approach are then treated with chemotherapy ± rituximab. A recently published prospective trial of 74 patients followed this type of approach. Patients who failed to respond to upfront RIS were eligible for protocol therapy, which consisted of 4 weekly infusions of rituximab, followed by 4 cycles of CHOP chemotherapy. This approach resulted in excellent overall and complete response rates of 90\% and 68\%, respectively.\textsuperscript{74} These results appear improved in comparison to prior prospective studies of RIS + rituximab in which most patients who failed RIS + rituximab later went on to receive chemotherapy. The authors therefore argued for earlier application of chemotherapy in patients failing RIS. However, retrospective comparisons across phase II trials are subject to bias, and a direct comparison of RIS + rituximab (followed by chemotherapy if necessary) versus RIS (followed by rituximab + chemotherapy, if necessary) has not been performed to date.

**RADIATION OR SURGICAL THERAPY**

Localized therapy with radiation may be an option in certain clinical situations as an adjunct to RIS. Radiation therapy is also used for local treatment and may successfully treat CNS PTLD. Several studies have demonstrated low mortality rates and encouraging response rates.\textsuperscript{94,95} Surgical resection may be accomplished for isolated PTLD lesions, and tumor debulking may be necessary for treatment of complications such as bowel perforation.\textsuperscript{29}

**INVESTIGATIONAL APPROACHES**

Other areas of investigation include cytokine-based therapies, mammalian target of rapamycin (mTOR) inhibitors, adoptive T-cell therapy, and antiviral therapies. Anti-IL-6 monoclonal antibody therapy is an area under investigation since IL-6 levels are elevated in most PTLD patients.\textsuperscript{3} The use of mTOR inhibitors in management is a current area of exploration since activation of the mTOR signaling pathway in tissue is found in all PTLD subtypes. Furthermore, because of their immunosuppressant activity, mTOR inhibitors may have a dual role in management. For example, an mTOR inhibitor such as sirolimus can be utilized for post-transplant immune suppression, but may also have a therapeutic benefit for PTLD because of the anti-lymphoma properties of mTOR inhibitors.

Adoptive T-cell therapy with EBV-specific cytotoxic T-cell lymphocytes (CTL) has been used successfully, particularly in HCT-related PTLD.\textsuperscript{96–99} In post-HCT PTLD, CTLs from the donor target the B-cell tumors of donor origin. In a recent study, EBV-CTLs resulted in a complete or partial remission in 68\% of biopsy-proven EBV-positive PTLD after HCT. About half of these patients had received rituximab with either no response or a short-lived response. In those who responded, the infusion resulted in an exponential increase in EBV-specific CTLs followed by resolution of the EBV viremia.\textsuperscript{100} PTLD after SOT is of recipient origin and CTLs from the recipient are necessary to effectively target EBV-infected B cells.\textsuperscript{3} It is possible to create autologous anti-EBV-specific CTLs from recipients who are EBV-seropositive before transplantation, although this may take 10 to 14 weeks. Autologous CTL have been shown to reduce viral load and induce regression of established PTLD.\textsuperscript{101,102} Using autologous EBV-specific CTL combined with chemotherapy or rituximab has led to complete response in PTLD patients unresponsive to RIS.\textsuperscript{103} Though allogeneic EBV-specific CTLs have been used, they must be closely HLA-matched to prevent their rejection.\textsuperscript{104}

There is no clearly proven benefit of antiviral therapy in the treatment of PTLD. Acyclovir and ganciclovir are thymidine kinase inhibitors which decrease lytic viral replication of EBV-infected cells, ultimately lowering viral load and preventing EBV infection of memory B cells.\textsuperscript{3,105} However, these agents are ineffective against...
latent EBV infection, since they do not attack cells in the latent phase or transformed B cells. This is due to the fact that EBV transformed cells do not express thymidine kinase, which is necessary to metabolize these antiviral agents into their active form. A new and developing approach to this problem is the use of arginine butyrate, which induces thymidine kinase expression in EBV-infected cells, thereby making them susceptible to ganciclovir.

**PREVENTION**

Several studies have examined different approaches to target patients at risk for PTLD to ultimately reduce its incidence. Risk factors utilized to identify such patients have included primary EBV infection or rising EBV viral load, type of allograft, and high doses of immunosuppressants. Those at a higher risk may require increased surveillance for PTLD. Monitoring viral load is one strategy under development. A rise in EBV viral load over a short time course or positivity in an initially EBV-negative patient is concerning. However, only a minority of those with elevated EBV loads actually develop PTLD. In addition, there is often discordance between the viral load and PTLD development. For example, some PTLD patients may have low EBV viral loads. Additional studies are needed to examine EBV viral load and its relationship to PTLD. If high-risk patients could be reliably identified, preventive techniques might include minimization of immunosuppression, infusion of EBV-specific CTLs, or the use of new antiviral strategies. One study used CTLs for prophylaxis by identifying high-risk patients undergoing HCT. None of the patients who received CTLs prophylactically developed PTLD. Antivirals decrease lytic replication of EBV-infected cells, ultimately lowering the viral load and preventing EBV infection of memory B cells. Comparisons of PTLD incidence between those receiving antiviral therapy and those without it demonstrate that both acyclovir or ganciclovir may decrease its risk. However, PTLD has been reported in those receiving antivirals, and therefore the use of antiviral agents for this purpose remains controversial. Strategies for early detection remain an important tool deserving further investigation.

**CONCLUSION**

Despite definite advances in treatment, PTLD remains a serious and sometimes fatal complication in patients undergoing SOT and HCT. Future studies, ideally prospective randomized clinical trials, are needed to determine the optimal timing and combination of RIS, rituximab, and combination chemotherapy. In addition, prospective clinical trials are needed to explore novel investigational approaches such as antiviral agents, adoptive T-cell therapy, and mTOR inhibitors for both prophylaxis and treatment of PTLD.
Post-transplant Lymphoproliferative Disorders


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