REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Post-Transplantation Lymphoproliferative Disorders in Adults

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POST-TRANSPLANTATION LYMPHOPROLIFERATIVE DISORDERS (PTLDS) ARE defined as lymphomas that occur after transplantation (Fig. 1). Recipients of solid-organ or allogeneic hematopoietic stem-cell transplants have an increased risk of cancers related to immunosuppression and the Epstein–Barr virus (EBV) — in particular, lymphomas.[1,2] Although lymphoproliferative disorders were initially reported to be a rare complication of transplantation, observations during the past decade have shown that they are not uncommon and are associated with poor outcomes. Lymphoma accounts for 21% of all cancers in recipients of solid-organ transplants, as compared with 4% among women and 5% among men in an immunocompetent population.[3] Important advances in diagnosis and treatment have been made after two consensus conferences.[4,5] This review outlines our current understanding of the epidemiology of and risk factors for PTLD, the pathogenesis of these disorders, and current approaches to diagnosis, staging, and treatment.

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EPIDEMIOLOGY AND RISK FACTORS

MAGNITUDE OF THE PROBLEM

Since the first description of five cases in 1969 by Penn et al., PTLD has become a serious complication of both solid-organ and hematopoietic stem-cell transplantation.[6] Data from large transplantation registries and single-center studies during the past 10 to 15 years have shown an increased incidence of PTLD and significant associations with morbidity and mortality.[1,2] The increasing incidence of newly diagnosed PTLD in the past two decades is related to growing numbers of transplantations, an older age of donors and recipients, use of new immunosuppressive agents and regimens, the introduction of haploidentical hematopoietic stem-cell transplantation (in which the donor and recipient share exactly one HLA haplotype), increased awareness of the disorder, and improved diagnostic tools.

Several measures have been used to determine the incidence of PTLD in the transplant-recipient population. Most large transplantation registries have reported standardized incidence ratios (SIRs), representing the observed number of lymphoma cases in the population of transplant recipients divided by the expected number of cases in the population of persons who are not transplant recipients. Overall, these studies revealed SIRs of approximately 10 for non-Hodgkin's lymphoma and 4 for Hodgkin's lymphoma among solid-organ transplant recipients.[7] Among recipients of hematopoietic stem-cell transplants, the incidence depends on the donor type, with an overall incidence of 3.2% in a retrospective multicenter analysis.[2]

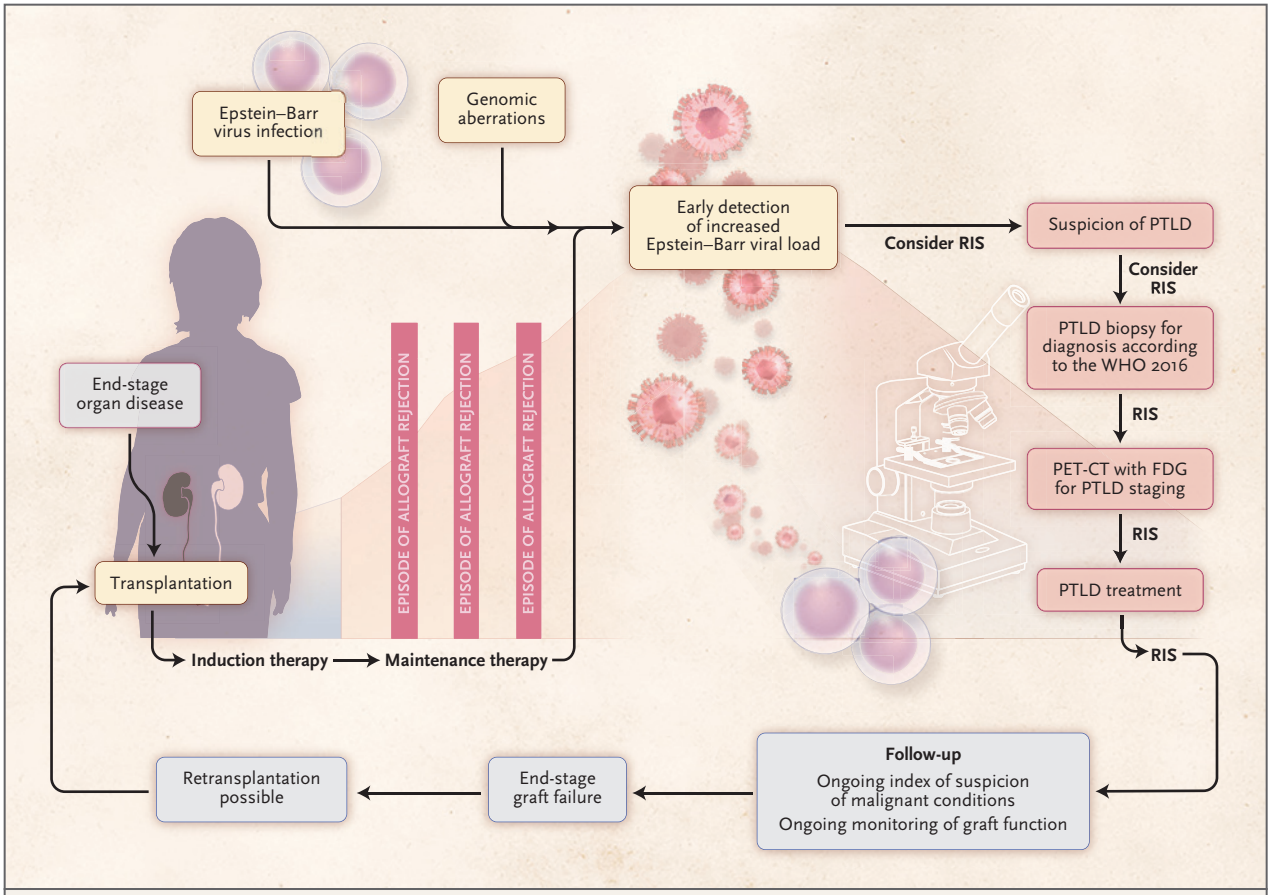


Figure 1. Development of Post-Transplantation Lymphoproliferative Disorder (PTLD) after Solid-Organ Transplantation.

Recipients of solid-organ transplants receive immunosuppressive therapy to prevent allograft rejection. Immunosuppressive therapy can be divided into induction therapy, administered in the peritransplantation period, and maintenance therapy, started at the time of transplantation and typically continued during the lifetime of the allograft. The induction regimen mainly consists of high-dose glucocorticoids and monoclonal or polyclonal T-cell–depleting and T-cell–nondepleting antibodies. Maintenance therapy often includes low-dose glucocorticoids, calcineurin inhibitors (cyclosporine and tacrolimus), antimetabolic agents (azathioprine and mycophenolate mofetil), and mammalian target of rapamycin (mTOR) inhibitors (everolimus and sirolimus). During the post-transplantation period, immunosuppressive therapy may be increased to manage episodes of allograft rejection (red bars). During this course of ongoing immunosuppression, Epstein–Barr virus (EBV) infection (both primary infection and reactivation) may lead to uncontrolled lymphocyte proliferation. In addition, genomic aberrations may occur, promoting lymphomagenesis. Early detection of an increased viral load in EBV-driven lymphomas offers an opportunity to try to preempt the development of PTLD by reducing immunosuppression, with or without other interventions. If this strategy fails or is not performed (preemptive strategies cannot be used in EBV-negative disease), PTLD can develop. If PTLD is suspected, a biopsy should be performed, with pathological confirmation according to the World Health Organization (WHO) 2017 classification. In addition, accurate staging is necessary. If immunosuppressive therapy has not been reduced, this should be done promptly, in most cases followed by antilymphoma treatment. After completion of treatment, reduction of immunosuppression (RIS) should be continued, if possible. If rejection occurs during follow-up, immunosuppressive therapy should be increased. Eventually, most patients have progression to end-stage graft failure (because of chronic allograft rejection or for other reasons). Limited experience has shown that retransplantation is feasible in patients with a history of PTLD. FDG denotes ^{18}F-fluorodeoxyglucose, and PET positron-emission tomography.

RISK FACTORS

Risk factors for the development of PTLD have been identified on the basis of varying levels of evidence. The risk is affected by the type of organ transplanted, with marked differences in the incidence among transplant recipients, depending on the transplanted organ. In the adult population, recipients of kidney transplants have the lowest incidence of PTLD (0.8 to 2.5%), followed by recipients of pancreatic transplants (0.5 to 5.0%), liver transplants (1.0 to 5.5%), heart transplants (2.0 to 8.0%), lung transplants

(3.0 to 10.0%), and multiorgan and intestinal transplants (≤20%).[8,9] For allogeneic hematopoietic stem-cell transplants, the incidence depends mainly on the degree of HLA matching and, hence, the need for T-cell depletion protocols before transplantation. However, the risk has been reported to be high with certain T-cell depletion procedures (relative risk, 8.4 to 15.8), whereas lower incidences are reported with the use of broad lymphocyte (T-cell and B-cell) depletion protocols (relative risk, 3.1).[10] As a consequence, the highest incidence of PTLD is observed with haploidentical allogeneic hematopoietic stem-cell transplantation (ranging from 0 with the use of post-transplantation cyclophosphamide as prophylaxis against graft-versus-host disease to >20% in cases of selective T-cell depletion). The next highest incidences are among recipients of transplants from unrelated donors (4 to 10%), umbilical-cord transplants (4 to 5%), and classic transplants from matched, related donors (1 to 3%).[2,9-12] An additional risk factor in hematopoietic stem-cell transplantation is a recipient age of more than 50 years (relative risk of PTLD, 5.1).[10]

Underestimation of the risk of PTLD remains a pitfall in interpreting these data if patients are not followed long-term. A recent study involving kidney-transplant recipients showed that combining registry data with review of pathological findings almost doubles the observed incidence of PTLD.[13] EBV seronegativity before transplantation in solid-organ transplant recipients is an important predisposing factor of PTLD, which develops primarily from the recipient's lymphocytes, leading to an increase in risk by a factor of 10 to 75, as compared with the risk among seropositive recipients.[14,15] This is the reason that PTLD is more common in children than in adults; primary EBV infection is the most common PTLD trigger in children. During the past two decades, in parallel with improved patient and graft survival, the incidence of PTLD has been characterized by a bimodal curve, with an initial spike (mostly involving EBV-positive transplant recipients) during the first year and a second, late spike (often involving EBV-negative recipients), which typically occurs 5 to 15 years after transplantation. In addition, there are a growing number of very late cases, developing more than 20 years after transplantation.[9,16-18]

The observation of a significant increase in the incidence of many infection-associated cancers, including lymphomas, among transplant recipients and patients with other immunosuppressed conditions (e.g., cancers associated with human immunodeficiency virus infection) suggests that an impaired immune system has a role in the pathogenesis of cancers in both patient populations.[19] The contribution of each immunosuppressive agent is not clear, since patients receive multiple agents in different doses and at different times in the course of the transplantation process. Induction therapy plays a major role in the early development of PTLD, whereas late development is likely to be related to cumulative immunosuppression. As a result of the temporary administration of immunosuppressive therapy, most cases of PTLD in recipients of allogeneic hematopoietic stem-cell transplants occur in the first year after transplantation and are derived from donor (EBV-infected) lymphocytes, with almost 100% association with EBV. T-cell depletion strategies and the type of donor are considered the strongest factors affecting risk.[10] Several other risk factors have been described, although their role in the development of PTLD is less clear (Table 1).

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

The clinical presentation of PTLD is heterogeneous, ranging from incidental asymptomatic findings to a fulminant presentation, including organ failure and spontaneous tumor lysis. The differential diagnosis includes allograft rejection (in particular, in the case of graft involvement) and infection or sepsis (especially if the patient has symptomatic disseminated disease). In contrast to many other aggressive non-Hodgkin's lymphomas, PTLD is characterized by a high incidence of extranodal involvement. In several large series, PTLD frequently involved the gastrointestinal tract (in 20 to 30% of cases), solid allografts (10 to 15%), and the central nervous system (5 to 20%).[2,9,20-22]

Although early-onset PTLD has characteristics that are distinct from late-onset PTLD (with early-onset cases more frequently characterized by EBV positivity and graft involvement and less often characterized by extranodal disease and a monomorphic subtype), risk factors and response to treatment are similar with early-onset

Table 1. Risk Factors for the Development of Post-Transplantation Lymphoproliferative Disorder.*

Variable	Risk after Solid-Organ Transplantation	Risk after Allogeneic HSCT
Established risk factors		
	Type of transplanted organ, relative risk: multiorgan and intestinal, 239.5; lung, 58.6; pancreas, 34.9; liver, 29.9; heart, 27.6; kidney, 12.6	Type of donor or donation, incidence: haploidentical, ≤20%; unrelated, 4–10%; umbilical cord blood, 4–5%; HLA-identical related, 1–3%
	EBV mismatch at time of transplantation (recipient EBV-negative, donor EBV-positive); relative risk, 10–75	
		Recipient age, >50 yr; relative risk, 5.1
	Intensity of induction immunosuppressive therapy and duration of maintenance therapy (including graft-rejection episodes); overall SIR, 10	Conditioning regimen (T-cell–depleting strategies, both in vivo and ex vivo; relative risk, 3.1–15.8); maintenance immunosuppressive medication (for chronic GVHD; relative risk, 2.0)
Strong evidence of risk		
	Increased risk associated with ATG, OKT3, tacrolimus, azathioprine, new agents (e.g., belatacept in EBV-negative transplant recipient)	
	Controversial degree of risk associated with alemtuzumab, cyclosporine, mTOR inhibitors	
	No increase in risk associated with mycophenolate mofetil, basiliximab, daclizumab	
Weak evidence of risk		
	Underlying disorder (HCV, cystic fibrosis, autoimmune hepatitis)	Underlying disorder (primary immunodeficiency, advanced Hodgkin's lymphoma)
	Race or ethnic group (risk in descending order): white, black, African	
		Prior splenectomy
	Monoclonal gammopathy of undetermined significance (in recipient)	Monoclonal gammopathy of undetermined significance (in recipient or donor)
	Non-EBV infection (HCV or CMV infection)	Non-EBV infection (CMV infection)
	Older donor age and younger recipient age	
	Cytokine gene polymorphisms	
	HLA alleles, haplotypes, mismatches, antibodies	HLA alleles, haplotypes, mismatches, antibodies

* ATG denotes antithymocyte globulin, CMV cytomegalovirus, EBV Epstein–Barr virus, GVHD graft-versus-host disease, HCV hepatitis C virus, HSCT hematopoietic stem-cell transplantation, mTOR mammalian target of rapamycin, and SIR standardized incidence ratio (representing the observed number of lymphoma cases in the overall population of transplant recipients, regardless of transplant type, divided by the expected number of cases in the population of persons who are not transplant recipients).

and late-onset disease.[16,23-25] The standard for the diagnosis of PTLD is histopathological examination and categorization according to the World Health Organization (WHO) 2017 classification, which distinguishes six subclasses of PTLD (Table 2): three types of nondestructive PTLD (plasmacytic hyperplasia, infectious mononucleosis–like PTLD, and florid follicular hyperplasia), polymorphic PTLD, monomorphic PTLD (B-cell, T-cell, or natural killer–cell types), and classic Hodgkin's lymphoma–like PTLD. An association with EBV infection is observed in almost all cases of nondestructive PTLD, more than 90% of cases of polymorphic and Hodgkin's lymphoma–like PTLD, and approximately half of monomorphic cases. From a pathological viewpoint, monomorphic PTLD cannot be distinguished from lymphomas with a similar lineage and cell of origin in immunocompetent patients, suggesting that the subclassification of these types should be the same.[26,27] Gene-expression profiling and immunohistochemical analysis have classified diffuse large B-cell lymphoma in immunocompetent patients on the basis of the cell of origin

— germinal center B cell or non–germinal center B cell.[28-30] In PTLD, EBV-positive cases are usually non–germinal center B-cell type, whereas the EBV-negative cases are more likely to be germinal center B-cell type.[27,31,32] Although an association with EBV is not required for the diagnosis of PTLD, an EBV-encoded RNA (EBER) in situ hybridization assay is recommended in all cases.[33] Preemptive monitoring of peripheral-blood Epstein–Barr viral load does not have diagnostic value, despite the widespread use of this test. The WHO classification has contributed to a more homogeneous approach to the diagnosis of PTLD by including various disease entities, but several factors are not covered by this mainly pathological classification, including transplant type (solid organ vs. hematopoietic stem cells), EBV status (positive vs. negative), and molecular-genomic features.[34]

After pathological confirmation of the diagnosis, accurate staging is mandatory. Current staging procedures for the type of lymphoma are used for PTLD. Although ^{18}F-fluorodeoxyglucose positron-emission tomography combined with computed tomography is highly sensitive for the detection of PTLD and has excellent discriminatory capability, its use in staging and in assessing the response to treatment requires prospective validation and is not currently recommended.[35]

PATHOGENESIS

ROLE OF EBV

Cases of PTLD were originally considered to be uniformly EBV-driven, but according to reports published in the past decade, up to 50% of PTLD cases that develop after solid-organ transplantation are not associated with EBV.[23] The pathogenesis of EBV-positive cases is clear, with an iatrogenic, immunosuppression-related decrease in T-cell immune surveillance as the major contributing factor. By expressing different latent antigens during B-cell development, EBV incorporates the normal B-cell program promoting proliferation and transformation of these cells. In normal circumstances, these antigens elicit a T-cell response that destroys the majority of EBV-infected B cells. This immunologic response is diminished in transplant recipients, resulting in B-cell transformation and development of lymphomas.[36] The patho-

Table 2. Classification of Post-Transplantation Lymphoproliferative Disorder (PTLD) by the World Health Organization (WHO).*

Characteristic	Nondestructive PTLD†	Polymorphic PTLD	Monomorphic PTLD	Hodgkin's Lymphoma–like PTLD
Underlying architecture	Nondestructive	Destructive	Destructive	Destructive
Composition	Plasma cells, small lymphocytes, immunoblasts	Complete spectrum of B-cell maturation	Fulfills specific WHO criteria for NHL; mantle-cell and follicular NHL are not considered PTLD	Fulfills specific criteria for classic Hodgkin's lymphoma
Immunohistochemical features	No diagnostic value	Mixture of B cells and T cells	Monoclonal population 90% DLBCL, mostly CD20+ (majority ABC type)	CD20–, CD30+; most cases CD15+
EBV association	Almost 100%	>90%	Both EBV-positive and EBV-negative	>90%
Clonality	No in most cases	Variable	Yes	Yes
Molecular genetic findings	None	Variable (BCL6 somatic hypermutations)	Differences between EBV-positive (genomic stable) and EBV-negative (similar to DLBCL in immunocompetent patients)	No information available
Clinical features	Mostly early PTLD	Variable	Both early and late PTLD	Possible increase in incidence of late-onset Hodgkin's lymphoma after allogeneic HSCT

* Information is from Swerdlow et al.[26,27] ABC denotes activated B-cell, DLBCL diffuse large B-cell lymphoma, NHL non-Hodgkin's lymphoma, and WHO World Health Organization.
† Nondestructive PTLD includes plasmacytic hyperplasia PTLD, infectious mononucleosis–like PTLD, and florid follicular hyperplasia PTLD.

genesis of EBV-negative cases of PTLD is less clear. Proposed hypotheses include hit-and-run EBV infection (i.e., EBV infection that initiates the pathogenesis of PTLD and then disappears), infection with cytomegalovirus or another, unknown virus, persistent antigen stimulation by the graft, and long-term immunosuppression.

DIFFERENCES BETWEEN EBV-POSITIVE AND EBV-NEGATIVE PTLD

Molecular-genomic studies of the diffuse large B-cell lymphoma subtype have revealed clear differences between EBV-positive and EBV-negative PTLD. Whereas EBV-negative cases share many genomic and transcriptomic features with diffuse large B-cell lymphoma in immunocompetent patients, EBV-positive cases have fewer genomic abnormalities, an observation that is consistent with the development of many EBV-positive cases very soon after transplantation. The more complex copy-number aberrations observed in EBV-negative cases reflect the typical accumulation of genomic alterations seen in diffuse large B-cell lymphoma in immunocompetent patients.[37-39] From a genomic point of view, EBV-negative PTLD may therefore be considered a lymphoma occurring coincidentally in a transplant recipient. The same applies to the more rare (mostly EBV-negative) T-cell subtypes, which share alterations with T-cell lymphomas in immunocompetent patients.[40] Future studies, including whole-exome or genomewide sequencing and studies of the role of EBV-associated microRNAs, may further define the complex pathogenesis of PTLD and lead to a more precise molecular–genomic classification of both EBV-positive and EBV-negative PTLD.

Although the molecular genetic separation between EBV-positive and EBV-negative cases of PTLD is clear, the clinical consequences of EBV status are less clear. Tumor EBV status is not prognostic or predictive with respect to treatment response in adults with PTLD.[23,41] However, molecular-genomic data provide the basis for initiating clinical trials of targeted therapy for both EBV-positive and EBV-negative cases of PTLD. An additional clinical observation arguing against two distinct subtypes is the finding that a proportion of both EBV-positive and EBV-negative cases of PTLD respond to a reduction in immunosuppressive therapy as the sole intervention.[42]

EBV MONITORING FOR PREEMPTIVE THERAPY

The risk of EBV-positive PTLD is associated with the type of organ transplanted, the pretransplantation EBV serostatus of the recipient and donor, and the interval between transplantation and diagnosis of PTLD.[14] Monitoring for preemptive treatment of PTLD is usually accomplished by measuring the viral load with the use of polymerase-chain-reaction amplification of EBV DNA from peripheral blood.[43-45] Transplant recipients with PTLD have a significantly higher viral load than recipients without PTLD, and a higher or rapidly increasing viral load is associated with an increased risk of PTLD.[46,47] The major drawback of this approach is the lack of standardized time points for monitoring, cutoff values, and sources of samples, although several efforts have been made to address the problem. As a result of this heterogeneity, reported positive and negative predictive values have varied widely for both solid-organ transplantation (28 to 100% and 75 to 100%, respectively) and allogeneic hematopoietic stem-cell transplantation (25 to 40% and 67 to 86%, respectively).[48-51] Cell-free plasma EBV DNA has been reported to be a better marker of EBV-positive disease than EBV DNA from peripheral-blood mononuclear cells.[47,52] Several preemptive approaches, including reducing immunosuppressive therapy, administering rituximab, and adoptively transferring EBV-specific T cells, have reduced the incidence of PTLD among both solid-organ and hematopoietic stem-cell recipients.[53,54] A preemptive approach should be considered only for transplant recipients with a high risk of PTLD, but the high-risk category has not been yet been defined by consensus.

TREATMENT

Therapeutic strategies for PTLD, which differ from the management of lymphoproliferative disorders in immunocompetent patients, include reduction of immunosuppression, surgical extirpation of localized disease, local radiation therapy, rituximab monotherapy, immunochemotherapy, chemotherapy, stem-cell transplantation, and cellular immunotherapy. An overview of treatment options is provided in Table 3.

Table 3. Current Regimens for the Treatment of PTLD.*

Treatment	Mechanism of Action	Indications	Considerations
Reduction of immunosuppression	Restoration of T-cell function — in particular, EBV-specific T-cell response	Preemptive therapy in high-risk transplantations; first-line treatment for all PTLD subtypes	High response rates for nondestructive PTLD; responses also observed in EBV-negative cases; takes time, which may not be feasible in very aggressive cases; not indicated as sole up-front therapy for monomorphic non-DLBCL subtypes; risk of organ rejection (can be performed more aggressively with kidney and pancreatic transplants than with other transplant types); less effective after allogeneic HSCT than after SOT
Surgery	Reduction of tumoral mass	Limited stage of disease; palliative care	Combined with reduction of immunosuppression; rapid symptom relief
Radiotherapy	Reduction of tumoral mass	Limited stage of disease; after chemotherapy in HL; whole-brain radiotherapy in PCNSL if chemotherapy contraindicated; palliative care	Combined with reduction of immunosuppression; rapid symptom relief
Adoptive immunotherapy (EBV-specific cytotoxic T-cells)	Restoration of EBV-specific T-cell response	Relapsed or refractory PTLD; possible preemptive therapy	Only for EBV-positive cases; time-consuming, high costs, and limited availability; low toxic-effects profile (no risk of GVHD, in contrast to classic donor lymphocyte infusions)
Chemotherapy	Reduction of tumoral mass	For nondestructive PTLD, polymorphic PTLD, or monomorphic DLBCL in patients who do not have complete remission after reduction of immunosuppression plus rituximab; lymphoma-specific therapy for other (non-DLBCL) monomorphic subtypes	High response rates; risk of infection; reduced treatment-related morbidity and mortality over past two decades
Rituximab	Reduction of tumoral mass	First-line treatment (after reduction of immunosuppression) for nondestructive PTLD, polymorphic PTLD, or monomorphic DLBCL; combined with chemotherapy in all non-DLBCL, CD20+ monomorphic subtypes; role in preemptive therapy	Only for CD20+ PTLD; favorable toxic-effects profile; improves performance status before chemotherapy; risk of infection
Antiviral therapy	Targeting of EBV	Promising role in combination with viral thymidine kinase–inducing agents (e.g., the HDAC inhibitor arginine butyrate), but not further developed	No efficacy as monotherapy (absence of viral thymidine kinase expression in EBV-positive PTLD); only for EBV-positive cases
High-dose therapy and autologous HSCT	Reduction of tumoral mass	Relapsed or refractory PTLD	Feasible, but limited experience

* HDAC denotes histone deacetylase, HL Hodgkin's lymphoma, PCNSL primary central nervous system lymphoma, and SOT solid-organ transplantation.

REDUCTION OF IMMUNOSUPPRESSION

The cornerstone of the initial management of PTLD is to reduce immunosuppression in order to partially restore EBV-specific cellular immunity, without inducing graft rejection. Reduced immunosuppression leads to regression of PTLD in 20 to 80% of polyclonal or monoclonal cases. This wide variation is multifactorial.[55-57] The initial management strategy should include reduction of calcineurin inhibition (cyclosporine or tacrolimus) by at least 50% and discontinuation of antimetabolic agents (azathioprine or mycophenolate mofetil, although the latter does not seem to be associated with the development of PTLD).[57] For critically ill patients with extensive or life-threatening disease, all nonglucocorticoid immunosuppressive agents should be discontinued. In contrast to the staging of lymphoma in immunocompetent patients, restaging in transplant recipients is performed at 2 to 4 weeks, since responses occur early. Additional interventions should be considered if a partial remission is achieved or there is no response to a trial of reduced immunosuppressive therapy. Graft monitoring is essential during this period to allow early detection of allograft rejection. In the only prospective trial incorporating reduced immunosuppression in a sequential treatment protocol for PTLD related to solid-organ transplantation, 37% of the patients had acute rejection after immunosuppressive therapy was reduced.[56] EBV-negative disease is less responsive than EBV-positive disease to a reduction in immunosuppression, although responses have been reported.[9,42] Bulky disease (largest tumor deposit, >7 cm in diameter), an advanced stage (Ann Arbor stage III or IV), and older age (>50 years) are independently associated with a lack of response to reduced immunosuppression.[55]

RITUXIMAB

Rituximab, a monoclonal anti-CD20 antibody, has become a standard treatment in patients with nondestructive PTLD, polymorphic PTLD, or monomorphic diffuse large B-cell lymphoma–like PTLD who do not have a response to reduced immunosuppression. With rituximab administered as a single agent at a dose of 375 mg per square meter of body-surface area weekly for 4 weeks, the overall response rates after reduced immunosuppression and rituximab therapy are 44 to 79%, with complete remission rates of 20 to 55%[41,58-63] (Fig. 2A). In addition, risk-adapted extended treatment, with four additional rituximab doses, increased the complete response rate from 34% to 60.5% in one study.[61] Rituximab consolidation may be sufficient treatment for patients in complete remission after the standard 4-week course. In the PTLD-1 study, a prospective, multicenter trial involving patients with PTLD after solid-organ transplantation, the complete response rate was 25% (37 of 148 patients) after standard induction plus four courses of rituximab every 21 days (low-risk group).[41] A complete response predicted improved overall survival, prolonged time to progression, and improved progression-free survival. In addition, as compared with patients who had a complete remission with rituximab monotherapy followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) consolidation in the first cohort of the trial, the low-risk group in the cohort that received risk-stratified sequential treatment had a longer time to progression at 3 years of follow-up, although overall survival was similar.[63,64]

Figure 2 (facing page). Evolution of Rituximab-based Treatment Protocols for PTLD after Solid-Organ Transplantation.

Panel A shows the results of prospective phase 2 trials evaluating rituximab monotherapy. In one study, risk-adapted extended treatment, with four additional rituximab doses, increased the complete response rate from 34% to 60.5%.[61] Panel B shows the protocol for sequential treatment in the PTLD-1 trial.[63] Patients were enrolled in this portion of the trial from 2002 through 2008. Panel C shows the protocol in the PTLD-1 trial for risk-stratified sequential treatment.[41] Patients were enrolled in this portion of the trial from 2006 through 2014. Panel D shows that, on the basis of the PTLD-1 findings, a new multicenter, prospective trial (PTLD-2) is currently enrolling patients, with risk stratification based on the response to rituximab, International Prognostic Index (IPI) score, and type of organ transplanted (ClinicalTrials.gov number, NCT02042391). CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP-21 CHOP administered every 21 days; DHAOx dexamethasone, high-dose cytarabine, and oxaliplatin; G-CSF granulocyte colony-stimulating factor; IV intravenous; NR not reported; R-CHOP-21 rituximab plus CHOP-21; and SC subcutaneous.

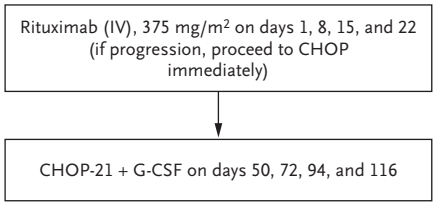
CHEMOTHERAPY

Immunochemotherapy is indicated in patients with B-cell PTLD who have not had a response to reduced immunosuppression and rituximab administered as a single agent.[41] Other indica-

A Prospective Phase 2 Trials with Rituximab Monotherapy

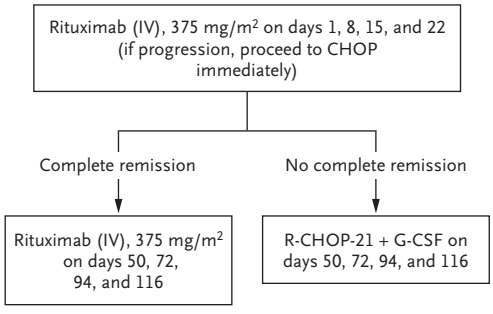
Study	No. of Patients	Overall Response Rate (complete response rate) %	Survival
Oertel et al.[58]	17	59 (53)	Overall survival at 3 yr, 56%
Blaes et al.[59]	11	64 (55)	Mean overall survival, 14 mo
Choquet et al.[60]	43	44 (28)	Overall survival at 1 yr, 67%
González-Barca et al.[61]	38	79 (34→60.5)	Overall survival at 27.5 mo, 47%
Trappe et al.[63]	70	60 (20)	Part of sequential treatment
Trappe et al.[41]	152	NR (25)	Overall survival at 3 yr, 91% (only low-risk patients treated with rituximab only)

B PTLD-1 Trial, Sequential Treatment



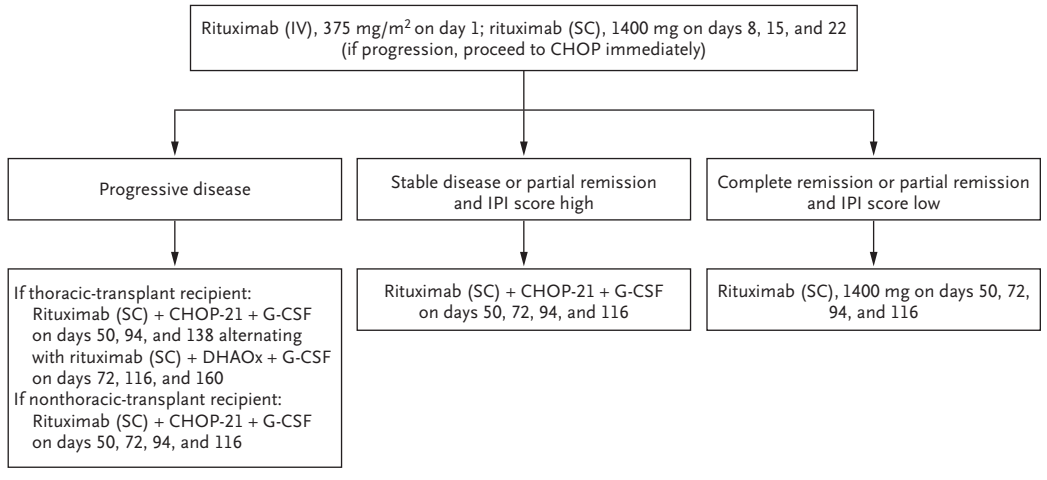
No. of Patients	74
Overall Response Rate	90%
Complete Response Rate	40%
Treatment-Related Mortality	11%
Median Overall Survival	6.6 Yr

C PTLD-1 Trial, Risk-Stratified Sequential Treatment



No. of Patients	152
Overall Response Rate	88%
Complete Response Rate	70%
Treatment-Related Mortality	8%
Median Overall Survival	6.6 Yr

D PTLD-2 Prospective Trial



tions for initial immunochemotherapy include specific histologic findings, such as peripheral T-cell lymphoma, Hodgkin's lymphoma, Burkitt's lymphoma, primary central nervous system lymphoma, and other uncommon lymphomas. These lymphomas must be treated with the standard-of-care approaches for the specific histologic features, which have clearly improved the prognosis for patients with these rare subtypes.[65-72] Although the value of reduced immunosuppression has not been established in these subtypes, it should certainly be considered and discussed with the transplant physicians, while taking into account the immunosuppressive properties of

chemotherapy itself and excess toxicity. Rituximab should be added in the treatment of all CD20-positive subtypes.

The outcome of PTLD treated with systemic chemotherapy in the 1980s and 1990s was poor, in part because of high treatment-related mortality.[73] Improved supportive care and the introduction of granulocyte colony-stimulating factors (G-CSF) has led to improved outcomes, although treatment-related mortality from infection remains high (31% in one retrospective trial[74]). The PTLD-1 trial showed the efficacy and safety of rituximab at a dose of 375 mg per square meter per week for 4 weeks, followed by CHOP every 3 weeks with G-CSF support.[63] In the second part of this trial, a risk-stratified sequential treatment approach was used, with rituximab plus CHOP (R-CHOP) administered every 3 weeks for four cycles with G-CSF support in patients who did not have a complete response to rituximab alone. The overall response rate was 88%, with 70% of the patients with any response having a complete response at the end of the treatment and a treatment-related mortality of 8% (Fig. 2B and 2C). In this trial, supportive treatment with G-CSF after R-CHOP was obligatory, and *Pneumocystis jirovecii* prophylaxis was recommended.[41] On the basis of the excellent results of this trial, reduced immunosuppression and risk-stratified sequential treatment are widely considered the standard of care for polymorphic and monomorphic diffuse large B-cell lymphoma–like PTLD (irrespective of EBV status) after solid-organ transplantation.

ADOPTIVE IMMUNOTHERAPY

EBV-specific cytotoxic lymphocytes (CTLs) are capable of inducing a strong EBV-specific cellular immune response.[36] A strategy of adoptive immunotherapy, using donor lymphocyte infusions, was first described for the treatment of PTLD after allogeneic hematopoietic stem-cell transplantation, which generally arises from donor cells, unlike PTLD in recipients of solid-organ transplants. However, the administration of donor lymphocyte infusions was associated with a high risk of graft-versus-host-disease.[75] In the past decade, expanded EBV-specific CTLs have been infused as part of prophylactic, preemptive, and therapeutic strategies, with autologous CTLs (in the case of recipient-derived PTLD) and allogeneic CTLs (isolated from the donor or from a bank of partially HLA-matched donors).[76] In addition, several new approaches have been developed, including adoptive transfer of pamidronate-expanded Vγ9Vδ2 T cells and tacrolimus-resistant, engineered CTLs, which provide treatment options for patients with PTLD without requiring reduced immunosuppression.[77] Indeed, on the basis of data from adoptive transfer of genetically engineered chimeric antigen receptor T cells, immunosuppression may enhance the engraftment of transferred T cells.

NEW STRATEGIES

New therapeutic options with high efficacy and minimal toxic effects remain a need for patients with PTLD in whom initial therapy fails. Table 4 lists potential new treatment options for these indications.[78-83] These treatments are considered experimental and need to be evaluated in prospective clinical trials. Particular attention should be given to differentiating between treatments for EBV-positive disease and those for EBV-negative disease and to incorporating molecular information and predictive or prognostic biomarkers in transplant recipients.

PROGNOSIS

The introduction of rituximab, the administration of lymphoma-specific regimens, and better supportive care have improved the outcome for patients with PTLD.[41,71,72] In the PTLD-1 trial (Fig. 2), 70% of the patients had a complete remission, with a median overall survival of 6.6 years, which was superior to survival for historical controls.[41] Prognostic scores have been published, but small samples, heterogeneous patient characteristics, different treatment protocols, and lack of validation remain major obstacles in their clinical use. On the basis of a French registry of 500 cases of PTLD after kidney transplantation, a prognostic score was proposed, which takes into consideration five variables (age, serum creatinine level, lactate dehydrogenase level, PTLD localization, and histologic features).[21] Although validated in an independent, smaller, single-center study, this new score was not superior to the classic International Prognostic Index (IPI).[84] The IPI score, which consists of five variables (age, performance status, stage, lactate dehydrogenase level, and number of extranodal sites), is widely used by hematologists and oncologists for identification of prognostic subgroups in aggres-

Table 4. Future Strategies for the Treatment of PTLD.*

Treatment	Compound	Considerations
BTK inhibition[78]	Ibrutinib	May also be active in GVHD and graft rejection; promising activity in ABC-type DLBCL
Inhibition of PI3K and mTOR[79]	Idelalisib (PI3K inhibitor); sirolimus (rapamycin) and everolimus (mTOR inhibitors)	Strong in vitro evidence of involved pathways; mTOR inhibitors also have strong immunosuppressive activity, but their use in treatment of PTLD is controversial
Proteasome inhibition[80]	Bortezomib	In particular, may be useful for early PTLD after allogeneic HSCT
Radioimmunotherapy[81]	^{90}Y-ibritumomab, tiuxetan	Effective in small pilot trial (SOT)
Checkpoint inhibitors[82]	Pembrolizumab, nivolumab	CTLA-4 pathway: contraindication, given high risk of (fatal) acute rejection; PD1 or PDL1 pathway: lower risk of acute rejection; should currently be considered only in clinical trials
Anti-CD30 therapy[83]	Brentuximab vedotin	Expression of CD30 in 85% of all PTLD subtypes; responses described in case reports

* BTK denotes Bruton's tyrosine kinase, CTLA-4 cytotoxic T-lymphocyte–associated antigen 4, PD1 programmed death 1, PDL1 programmed death ligand 1, and PI3K phosphoinositide 3-kinase.

sive lymphomas.[85] The prognostic value of the IPI was established in the PTLD-1 trial, with thoracic transplants and inadequate response to rituximab induction as additional factors indicating a poor prognosis.[64] A multicenter, prospective trial that incorporates these prognostic factors (PTLD-2) is ongoing (ClinicalTrials.gov number, NCT02042391) (Fig. 2D).

Retransplantation after diagnosis and treatment of PTLD is feasible in certain cases, although it seems reasonable to wait at least 1 year after treatment for PTLD.[86] In a French study, 52 kidney-transplant recipients underwent 55 retransplantations after PTLD. The median time between the diagnosis of PTLD and retransplantation was 90 months (range, 28 to 224), with only one case of PTLD developing after retransplantation.[87]

CONCLUSIONS

PTLD is one of the most serious complications of transplantation and is a consequence of therapeutic immunosuppression. New insights into the biology of PTLD and the role of EBV infection, improvements in immunosuppressive strategies for transplantation, advances in the treatment of PTLD, and the application of new molecular-genomic techniques have led to more sophisticated diagnostic and therapeutic approaches that are improving outcomes for patients with PTLD.

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