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Review Article

Post-Transplant Lymphoproliferative Disorders Arising after Allogeneic Hematopoietic Cell Transplantation: A Comprehensive Review

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Abstract

Post-Transplant Lymphoproliferative Disorder (PTLD) is a heterogeneous disorder that complicates both Solid Organ Transplantation (SOT) and Allogeneic Hematopoietic Cell Transplantation (allo-HCT). While the characterisitcs of SOT and HCT- PTLD are similar, important differences include lower incidence, early onset, rare graft involvement and donor origin for HCT-PTLD. Up to 10-20% of PTLD cases can lack tissue expression of EBV (EBV- PTLD); the response of EBV- PTLD to reduction in immunosuppression and treatment with rituximab is similar to that of EBV+ PTLD. In the allo-HCT, advanced age, T cell depletion (*in-vivo* or *ex-vivo*), use of unrelated and cord blood donors as the graft source, and transplant from HLA mismatched donors, are each associated with an increased incidence of PTLD. However, these risk factors cannot be easily extrapolated, as for example use of post-transplant cyclophosphamide for GvHD prophylaxis in the haploidentical allo-HCT is not associated with an increased risk of PTLD. While most PTLD arise from B cells, T or NK-cell PTLD constitute approximately 10-15% of all PTLD and are associated with extranodal involvement, aggressive course and poor survival. The revised World Health Organization (WHO) classification from 2016 categorizes PTLD into 6 subgroups, ranging from plasmacytic hyperplasia to classical Hodgkin lymphoma. Serial EBV DNAemia monitoring by PCR is effective in facilitating diagnosis but early recognition due to elevated EBV DNAemia alone has failed to significantly improve outcomes. It is essential to confirm the diagnosis and determine PTLD subtype by biopsy in order to deliver the most appropriate therapy as anti-CD20 monoclonal antibody therapy is generally effective but not for the PTLD subtypes of classical Hodgkin lymphoma PTLD. New approaches include cellular therapy with EBV-specific cytotoxic T lymphocytes.

Keywords: Epstein-Barr virus; PTLD; Allogeneic hematopoietic transplant; Solid organ transplant

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Introduction

Post-Transplant Lymphoproliferative Disorder (PTLD) is a heterogeneous condition with widely variable manifestations ranging from an infectious mononucleosis-like condition or a polyclonal B cell hyperplasia, to the development of a malignant lymphoma. While it is recognized that Epstein-Barr Virus (EBV) *de novo* infection or reactivation and chronic immunosuppression are predisposing factors, study of this disorder is complicated due to significant diversity of underlying disorders, clinical heterogeneity, and lack of prospective trials [1,2].

There is considerable overlap as reported in the literature regarding PTLD arising after SOT and that arising after allo-HCT [3-12]. In this review we focus on post HCT-PTLD to discuss pathogenesis, classification, diagnosis, risk factors, therapeutic strategies, prognosis, outcomes and future initiatives. The emphasis will be on unique aspects of PTLD as it relates to HCT, including EBV-negative PTLD, T or NK-cell PTLD, and risk factors in the contemporary era [13-40]. In absence of a clear information related to HCT-PTLD we clarify shared data from a SOT-PTLD.

Pathogenesis

PTLD represents a spectrum of lymphoproliferative states ranging from benign, reactive polyclonal hyperplasia to a fulminant malignant lymphoma. Most often, the inciting factor is reactivation of Epstein-Barr Virus (EBV) or human herpesvirus-4, a ubiquitous herpesvirus in human hosts. The pathogenesis of EBV+ PTLD is complex and is dependent on the life cycle of EBV, the EBV serostatus of the donor and recipient, and the capacity of the allo-HCT recipient to mount a protective immune response that limits viral replication. The pathogenesis of EBV- PTLD is less well understood but similarly reflects an impaired capacity of the allo-HCT recipient to appropriately recognize transformed populations of B lymphoblasts. In absence of data from allo-SCT, we herein discuss data from SOT.

EBV oncogenicity and transcription

Expression patterns of EBV latent genes are classified into 3 categories (Latency I, II, or III), and can be associated with different stages of EBV infection as well as different PTLD disorders (Table 1). For example, PTLD arising early after allo-HCT often is associated with a latency expression pattern III (EBNA-1, LMP-1,-2, and EBNA-2, -3A, -3B, -3C, and –LP) which closely resembles that seen in acute infectious mononucleosis. In contrast, oligoclonal or monoclonal EBV-positive PTLD is associated with a more restricted EBV latency gene expression pattern (Latency I: EBNA-1, as seen in PT- Burkitt Lymphoma; Latency II: EBNA-1 and LMP-1, -2, as seen in PT-DLBCL) and typically occurs later in the post-HCT course [15-17]. EBNA2 is considered a master transcriptional regulator of both EBV- and cellular-derived genes. LMP-1 is the major oncogenic protein of EBV. LMP-1 mimics CD40, a costimulatory transmembrane molecule that provides a survival and proliferation signal of B cells. LMP-1 leads to B cell proliferation and differentiation *via* activation of NFκB, AKT, and MAPK signaling pathways as well as activating anti-apoptotic genes (e.g. BCL-2 and c-FLIP) and increasing cytokine production (e.g. IL-10 and CD40L) [18,19]. LMP-2A ensures the survival of infected B cells by activating the B Cell Receptor (BCR) *via* Spleen Tyrosine Kinase (SYK)-mediated survival signals [20]. Once infection of a memory B cell is complete, viral protein production is shut down in order to minimize the immunogenicity of the infected cell.

Reactivation cycle

EBV infection can immortalize resting B cells. When a healthy, immunocompetent individual is infected with EBV, the initial burst of infected B cell proliferation elicits immune responses that limit this proliferation. These immune responses are mediated by NK cells early on and then by CD8+ Cytotoxic T Lymphocytes (CTL), and the survival and function of CD8+ CTL is likely governed by the function and persistence of EBV-specific CD4+ T cells. EBV-infected cells, which express highly immunogenic EBV-derived antigens on the cell surface, are effectively eliminated predominantly by CTLs. However, the subset of infected memory B cells are not eliminated because there is little to no viral antigen expression on the cell surface leading to a lifelong reservoir for EBV. Intermittent viral reactivation can occur resulting in virus shedding into bodily secretions that leads to infection of new B cells. This reactivation cycle can lead to uncontrolled proliferation of infected B cells unless NK cell-, CD4+ T cell- and/or CD8+ T cell-mediated immune responses are elicited. While latency is the predominant phase in EBV-driven tumors, an uncontrolled lytic phase may play a role (at least in part) in the early

Table 1: Summary of EBV Genes Expressed during Different Latency Phase Types and their Associated Disorders [15-17].

Latency	EBV Genes Expressed	B Cell Stage	Associated Disorders
III	EBER1-2, EBNA2, EBNA3A-C, EBNA-LP, LMP1, LMP2A-B	Activated B Cell Lymphoblast	• PT-DLBCL • AIDS-related Lymphoma* • Acute Infectious Mononucleosis
II	EBER1-2, EBNA1, LMP1, LMP2A	B Cells Undergoing GC Reaction	• PT-DLBCL • Classical Hodgkin Lymphoma
I	EBER1-2, EBNA1	Memory B Cell	• Burkitt Lymphoma-PTLD • Plasmablastic Lymphoma-PTLD

EBER: Epstein-Barr Virus-Encoded RNA; EBNA: Epstein - Barr virus Nuclear Antigen; LMP: Latent Membrane Protein; PT-DLBCL: Post-Transplant Diffuse Large B Cell Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma; PTLD: Post-Transplant Lymphoproliferative Disorder; EBV: Epstein - Barr virus

stages of transformation by providing signals that result in immune evasion by inhibition of IFN-α production and by CTL suppression [21].

Role of T cells

In the early post-HCT interval, CD4+ and CD8+ T cell responses to herpesviruses (including EBV and CMV) may be quantitatively reduced and/or persistently dysfunctional [19]. This impaired T cell immunity early after HCT, makes patients vulnerable to EBV reactivation and, more importantly, uncontrolled B cell proliferation that can transform into a malignancy. Thus, PTLD occurs in allo-HCT patients most frequently during the period of greatest T cell deficiency, i.e. in the early post-HCT period. These cases of PTLD arise from donor transferred EBV infected B cells or infection of transferred B cells. In this situation, the myeloablative conditioning destroys most host B cells that serve as EBV reservoirs. There is evidence that preserving the balance between EBV directed T cells and latently EBV infected B cells protects against EBV PTLD. Recent approaches to achieve this with the a/b TCD platform include incorporating rituximab and CD19 depletion to eliminate donor and recipient B cells [23-27].

Role of NK cells and Tregs

The role of NK cells in controlling PTLD has not been studied in allo-HCT patients. In a study of pediatric SOT patients, those who developed symptomatic PTLD had an increased number of CD56 dim/neg NK cells that were functionally impaired, whereas asymptomatic PTLD patients had increased numbers of CD56 high NK cells [28]. Also, a paucity of Regulatory T (Treg) cells has been found in PTLD lesions. While Tregs in the PTLD microenvironment may blunt anti-tumor responses, the lack of Tregs can lead to uncontrolled B cell proliferation, contributing to the development of PTLD [29].

EBV-negative PTLD

In contrast to PTLD of B-cell origin, only a minority of T-cell PTLD cases are EBV-positive (approximately one-third). EBV-negative PTLD is often monomorphic and typically resembles more aggressive lymphomas, such as DLBCL or Burkitt-like lymphoma it may be associated with viruses other than EBV, including HTLV-1, and HTLV-2, Human Herpesvirus-8 (HHV-8) and CMV. However, viremia is thought to be associated with immunosuppressive state and not necessarily the causative agent of the PTLD itself. Alternatively, EBV negative PTLD may be triggered by chronic antigen stimulation of donor cells driven by these and other infections; or it may arise coincidentally, as may occur in immunocompetent individuals. None of these theories, however, have been substantiated and more research into EBV-negative PTLD is needed. EBV negative PTLD is further discussed in a later section separately.

In contrast to the published experience in allo-HCT, EBV-positive PTLD after SOT has been associated with other viral infections. Specifically, donor-recipient CMV seropositivity mismatch has been shown to be associated with a 7-fold increase in PTLD following liver transplantation [31]. In addition, Hepatitis C Virus (HCV) and Human Herpes Virus 8 (HHV8) have been reported as risk factors for PTLD in heart and kidney transplant recipients [32,33].

In summary, EBV + PTLD arises either after *de novo* infection or viral reactivation in the immune incompetent host. Reactivation occurs when EBNA2 upregulates growth factors and functions as a transcript regulator for the expression of LMP-1 (which is the major oncogenic protein of EBV) and LMP-2. While EBV+ PTLD typically express the latency III EBV expression pattern, some PTLD can express a more restricted set of EBV genes characterized by Latency I and Latency II programs. Inder normal circumstances, EBV infected B lymphocytes are controlled by cytotoxic T cells, but if the immunity is impaired, EBV transformed cells can proliferate and lead to PTLD.

Classification

Over the past decade, the classification of PTLD has evolved. After it is proven *via* histology, PTLD needs to be categorized as precisely as possible by using the World Health Organization (WHO) classification system that was revised in 2016 [3,4]. The WHO classification system assigns categories based on morphology not EBV status. The earlier WHO system, developed in 2008, grouped PTLD into plasmacytic hyperplasia, infectious mononucleosis, polymorphic, monomorphic and Hodgkin-like. The current system, updated in 2016, categorizes PTLD into six types: 1) Plasmacytic; 2) Infectious mononucleosis; 3) Florid follicular hyperplasia (changed from the 2008 WHO classification in 2013); 4) Polymorphic; 5) Monomorphic (B- and T-/NK- cell types); and 6) Classical Hodgkin lymphoma (Table 2) [4]. Mutational analyses of both poly- and mono-morphic PTLD have demonstrated different genetic profiles as compared to lymphomas seen in immunocompetent hosts. Within the group of monomorphic PTLD, the different histologic lymphoma entities (i.e. diffuse large B-cell lymphoma, Burkitt lymphoma and plasmablastic lymphoma) should be distinguished and stratified according to

Table 2: World Health Organization (WHO) Classification of PTLD revised in 2016 [4].

• Plasmacytic hyperplasia PTLD
• Infectious mononucleosis PTLD
• Florid follicular hyperplasia PTLD
• Polymorphic PTLD
• Monomorphic PTLD (B- and T-/NK- cell types)
• Classical Hodgkin lymphoma PTLD

lymphoma subtype using standard Lugano criteria because of the implication for management and outcomes [4,11]. EBV-positive and EBV-negative PTLD have distinct biologic, genetic, and molecular profiles. For example, the majority of EBV-positive DLBCL PTLD are of non-Germinal Cell (GC) B origin. Non-GCB DLBCL cases characteristically have expression of NFKB pathway intermediates, which are most likely induced by EBV. In comparison, cases of EBV-negative DLBCL have genetic features in common with those that arise in immunocompetent patients. Because of these differences, EBV status needs to be included in future studies and clinical trials in order to further stratify PTLD patients. It should be noted that not all post-transplant lymphoproliferative disorders can be considered PTLD. Indolent B-cell lymphoma such as follicular lymphomas and MALT lymphomas in allograft recipients are designated as they are in the normal host and not considered a type of PTLD.

In summary, PTLD is currently classified based on morphology and not based on EBV status. EBV-negative DLBCL characteristics are similar to those seen in immunocompetent patients.

Clinical presentation and diagnosis

Current and historic trials accept viremia in conjunction with consistent imaging as probable PTLD. However, tissue confirmation helps confirm diagnosis and facilitates management. Patients may be asymptomatic at presentation and the clinical signs and symptoms of PTLD are nonspecific and variable. Patients with PTLD may have unexplained fevers, lymphadenopathy, CNS symptoms such as headache and confusion, diarrhea, or a combination of these findings. In rare instances, PTLD may present as a fulimant systemic disease with features of septic shock and/or Hemophagocytic Lymphohistiocytosis (HLH). Given the challenges of diagnosis, clinical suspicion should prompt an evaluation for PTLD, especially in high-risk patients or in the setting of rising serum EBV PCR copies. It should be noted that absence of a positive EBV PCR does not preclude the presence of PTLD.

EBV testing methodologies

While detection of EBV has been evaluated in both plasma and whole blood, the later is more sensitive [34]. Center to center variability in viral load testing makes the use of specific thresholds difficult. Only recently, DNA viral load measurements have been standardized, using International Units (IU) per ml blood or plasma. The introduction of these WHO quantitative international standards will help reduce this variability [34,35]. Data are needed regarding the likelihood of developing PTLD or fatal PTLD above a certain threshold of DNA measured in IU/ml, as most available data have been generated using institutional, presumably non-standardized, assays (reporting EBV DNA copies/ml) which give highly variable results [36]. Despite this limitation, some authors recommend pre-emptive therapy with rituximab for specific viral loads (see management section).

Imaging evaluation

Imaging can help guiding further diagnostic testing once PTLD is confirmed. In patients presenting with signs or symptoms suggestive of PTLD or biopsy-confiremd PTLD, studies have shown 18F-Fluorodeoxyglucose Positive Emission Tomography/ Computed Tomography (FDG-PET/CT) to have high sensitivity (88-90%), specificity (87-91%), positive predictive value (85 -91%) and negative predictive value (87-93%) to confirm biopsy-proven PTLD, or to distinguish PTLD from other disease entities [8,9]. The majority of these patients had undergone SOT (*versus* allo-HCT). Investigators reporting a recent study of 25 SOT patients showed that FDG-PET/CT detected bone marrow involvement at a higher sensitivity and similar specificity as a bone marrow biopsy [10]. Bone marrow involvement may have prognostic implications. As FDG-PET/CT is not sufficient for diagnosis of CNS involvement, dedicated imaging and/or CSF sampling should be performed in patients where there is concern for CNS involvement. Therefore, while FDG-PET/CT is clearly an important tool (particularly in the exclusion of a diagnosis of PTLD with a negative CT scan), the role of FDG-PET/CT in diagnosis, staging and assessing response continues to be refined.

In summary, while there are recommendations that EBV PCR of greater than 1,000 copies/105 PBMC should trigger preemptive therapy, this is not a universal recommendation. FDG-PET/CT is highly sensitive and specific; its role in assessment of PTLD continues to evolve. Current ongoing trials accept high viral load combined with characterstic radiologic findings as diagnostic criteria for EBV-PTLD.

Risk factors for PTLD

In addition to the strong correlation between EBV viral reactivation and the development of PTLD, other risk factors for a subject developing PTLD after allo-HCT have been identified and are summarized in (Table 3). The overall incidence of EBV viremia and PTLD after HCT varies by both pre and post transplant factors. The type of transplant, use and timing of screening methods and the assay sensitivity all contribute to incidence. Landgren, et al., [37], published the largest study addressing the risk for PTLD after HCT. They reviewed 26,901 patients from 271 centers worldwide and found that the majority of PTLD cases (83%) occured within 1 year after HCT. In a multivariable analysis, T-cell depletion of the donor marrow, ATG use, and unrelated or HLA-mismatched grafts were strongly associated with subsequent occurence of PTLD. In patients with at least three of the above features, the incidence of PTLD was 8.1%. Other identified risk factors included occurrence of acute or chronic Graft *Versus* Host Disease (GVHD), recipient age > 50 years, and undergoing a second HCT. Limitations of this analysis are inclusion of only bone marrow as a graft source, the vast majority of patients receiving a myeloablative regimen, and the early time period during which these HCTs were performed (1964 to 1994) [37]. In a more recent cohort of patients from Sweden (1996 to 2011) HLA mismatch, serological EBV mismatch (recipient -/donor+), reduced-intensity conditioning, acute GVHD grade II to IV, pretransplant splenectomy, and infusion of mesenchymal stromal cells were identified as significant risk factors for the development of EBV+PTLD [38]. A large contemporary analysis by the Infectious Diseases Working Party of the EBMT included recipients of peripheral blood stem cell grafts and reduced intensity HCT. Only 4% of cases developed after one year post-transplant with EBV viremia occuring on 0.1 -63% of transplant recipients and EBV PTLD developing in 1.16% of matched-family donor, 2.86% of mismatched family donor, 3.97% of matched unrelated donor, and 11.24% of mismatched unrelated donor recipients [30,40]. Recipients of cord blood transplant, especially those receiving ATG also have an especially high risk of developing EBV PTLD [39,40].

Table 3: Risk factors for PTLD following HCT.

Risk Factor	Reference
Profound and prolonged immunosuppression; T cell depleted allograft (*in vivo* and *ex vivo*)	(Patriarca 2013) [69] (Shapiro 1988) [41] (Witherspoon 1989) [114] (Curtis 1999) [115] (Podgorny 2010) [116] (Juvonen 2003) [117] (Mensen 2014) [118]
Unrelated donor HCT	(Juvonen 2003) [117]
HLA mismatch HCT	(Uhlin M 2013) [38] (Shapiro 1988) [41]
Umblical cord blood HCT	(Brunstein CG 2006) [31] (Dumas 2012) [119] (Sanz 2014) [111]
Recipient HLA-A26	(Reshef) [40]
Pre-transplant spleenectomy	(Sundin 2006) [122]
EBV serology mismatch between donor and recipient	(Sundin 2006) [122] (Uhlin M 2013) [38] (Kalra A 2018) [57]
Reduced intensitiy conditioning HCT	(Uhlin M 2013) [38] (Brunstein CG 2006) [31] (Dumas 2012) [119] (Sanz 2014) [111]
Rising EBV DNA copy in the blood	(van Esser 2001) [120] (Wagner 2003) [51] (Patriarca 2013) [69] (Kalra A 2018) [55]
GVHD	(Landgren O 2009) [37] (Uhlin M 2013) [38] (Shapiro 1988) [41]

HLA and PTLD: HLA and PTLD risk has not been documented in allo-HCT. In SOT however, investigators have demonstrated the relationship of PTLD with specific HLA polymorphisms. Reshef and co-workers 40 used a case-control study to compare 110 adult SOT affected recipients *versus* 5,601 unaffected subjects. Recipient HLA-A26 was highly associated with the likelihood of developing PTLD (OR 2.74; p = 0.0007). In Caucasian recipients, both recipient and donor HLA-A26 independently were associated with the emergence of PTLD (recipient A26: OR 2.99; p = 0.0004, donor A26: OR 2.81; p = 0.002). Recipient HLA-A26, B38 haplotype also was strongly correlated with a higher incidence of EBV-positive PTLD (OR 3.99; p = 0.001) [32]. HLA polymorphisms are important in modulating the risk for PTLD and may be useful in risk stratification and development of monitoring and prophylaxis strategies.

T-Cell Depletion

T-cell depletion has been associated with an increased incidence of PTLD. Delayed immune reconstitution is a hallmark of *in vivo* or *ex vivo* T cell depletion. After the administration of ATG, recovery of CD4+ T-cells is significantly delayed compared to non-ATG conditioned patients. T-cell depletion also is associated with delayed recovery of virus-specific T-cells [41,42]. An analysis of 26,000 patients from the CIBMTR database confirmed these risk factors. Selective T-cell depletion methods, such as ATG or sheep red blood cell rosetting, are associated with a higher risk of PTLD than are methods that remove both B-cells and T-cells, such as alemtuzumab [37]. The administration of ATG during the conditioning regimen also has been associated with PTLD; in one report the incidence of PTLD was as high as 8.1% [42-45].

In contrast to conventional T-cell depletion, Post-HCT Cyclophosphamide (PT-CY) as a *in vivo* T-cell depletion method used in haploidentical HCT does not appear to increase the risk of PTLD. Kanakry et al, [27] reported that none of the patients who received high-dose PT-CY in the setting of HLA-haploidentical, HLA-matched related or unrelated donor bone marrow HCT developed PTLD in the first year post allo- HCT. Similarly, recipients of alpha/beta T cell and CD19 depleted HCT who also receive rituximab as part of the conditioning regimen have an incidence of EBV disease of only 0.5%.

Non-EBV viruses and PTLD

There is a paucity of data reporting the association of non-EBV viruses and PTLD following allo-HCT. However, Cytomegalovirus (CMV) infection has been identified as a risk factor for EBV reactivation after allo-HCT. In this regard, Zallio and colleagues evaluated the utility of a pre-emptive management approach for EBV reactivation based on quantitative PCR monitoring of EBV DNA from blood and the administration of rituximab in patients at high risk for PTLD [44,101]. Consecutive allo-HCT patients who had received post-HCT rituximab for quantitative PCR (qPCR)-defined EBV reactivation, CMV reactivation was noted in 49 patients (49%). In addition, EBV reactivation occurred in 22 (45%) and 11 (22%) CMV-positive and -negative patients, respectively (p = 0.013). High risk for PTLD (as defined as >10,000 EBV copies/mL) was found in 14 (29%) and two (4%) CMV-positive and -negative patients, respectively (p=0.001). Median time between CMV and EBV reactivation was 26 days. In this study, multivariate analysis showed that CMV reactivation was the only independent variable associated with EBV reactivation.

In summary, T-cell depletion (*in vivo* or *ex vivo*) and unrelated or HLA-mismatched donor increase the risk of PTLD. ATG is associated with increased PTLD while alemtuzumab that removes both B-cells and T-cells reduces the risk of PTLD (compared to ATG). Other factors including, reduced-intesity conditioning, acute GVHD grade II to IV, pretransplant splenectomy, and infusion of mesenchymal stromal cells and recipient HLA-A26 are also associated with risk of PTLD.

Management

As discussed above, blood EBV-PCR surveillance is important for early detection of EBV reactivation. Based on the strong correlation between EBV reactivation in the form of viremia and the development of PTLD, evidence-based guidelines from the Second European Conference on Infections in Leukemia were developed in 2009. The guidelines recommend screening weekly for EBV-DNA for at least three months for high-risk allo-HCT recipients, as defined by unrelated or mismatched HCT, or *in- vivo* or *ex-vivo* T-cell depletion [14,64].

The management of PTLD needs to balance curing the patient of this life-threatening disease while preserving the allograft [46-60]. Generally, management strategies of PTLD involve decreasing and/or eliminating infected B-cells while attempting to preserve or increase EBV directed T cell immunity. Single agent rituximab and Reduction in Immune Suppression (RIS) are the most widely available first line approaches to achieve these goals. Other options include adoptive therapy with EBV-specific Cytotoxic T Lymphocyte (CTL)s or

Table 4: Studies of Prophylaxis, Preemptive, Empiric and Conventional Treatment Strategies for PTLD.

Strategy	N (number of evaluable patients)	Efficacy endpoints	Efficacy endpoint achieved (% patients)	Comment	Reference
Prophylaxis	55 *vs.* 68 ctrl[1] total patients	EBV DNAemia not high	86 *vs.* 51% (p<.001)	No impact on OS or mortality 2° PTLD; Prophylaxis was combinded with preemptive therapy	Dominietto 2012 [56]
		PTLD incidence	0% *vs.* 3% (N.S.)		
Preemptive Therapy	93 w high EBV	EBV undetectable	83%	2 patients died of PTLD	Garcia-Cadenas 2015 [52]
	55 w high EBV	EBV not high	91%	3 patients died of PTLD	Coppoletta 2011 [46]
	9 w high EBV	Mortality not 2° PTLD	44%		Pinana 2016 [67]
	35 *vs.* 30 ctrl[2] total patients	PTLD incidence	6 *vs.* 17% (N.S)	Impact on OS not reported	Blaes 2010 [53]
		Mortality 2° PTLD	3 *vs.* 7% (N.S)		
	35 *vs.* 30 ctrl[2] total patients	PTLD incidence	6 *vs.* 12% (N.S)	Impact on OS not reported	VanEsser 2002[54]
		Mortality 2° PTLD	0 *vs.* 6% (N.S)[3]		
Empiric Therapy	5 w PTLD	Regression	100%		Wagner 2004 [34]
	6 w PTLD	"CR"	67%		Kinch 2007 [123]
	6 w PTLD	Mortality not 2° PTLD	17%		Sanz 2014[111]
	266 *vs.* 199 ctrl[2] total patients (29 *vs.* 13 ctrl w PTLD)	Sustained. regression	75 *vs.* 73% (N.S)	No impact on OS	Kalra 2018 [57]
		PTLD incidence	11 *vs.* 6% (p=.06)		
		Mortality 2° PTLD	1% *vs.* 1% (N.S)		
Conventional Therapy	12 w PTLD	Sustained CR	67%		Faye 2001 [124]
	146 w PTLD	"Cure or Improvement"	63%	Review of case reports	Styczynski 2009 [48]
	144 w PTLD	Mortality not 2° PTLD	61%	Registry study	Styczynski 2013 [40]
	3 w PTLD	CR	100%	Pilot	Kuehnle 2000 [125]
	46 w PTLD	PFS and OS	68% and 84%	Prospective	Jiang X 2016 [126]
	8 w PTLD	CR	50%	Prospective	Comoli 2007 [127]

1. Controls were patients managed by preemptive therapy.
2. Controls were patients managed by regular therapy.
3. Significant difference only if patients with high EBV DNAemia were compared.

Abbreviations: OS: Overall Survival; PTLD: Posttransplant Lymphoproliferative Disorder; EBV: Epstein-Barr Virus; High EBV: High EBV DNAemia; CR: Complete Remission; Ctrl: Control; NS: Not Significant; Sust. Regression: Sustained Regression (regression not followed by later progression of PTLD); W: With; OS: Overall Survival; PFS: Progression Free Survival.

unselected Donor Lymphocytes (DLI), and chemotherapy. Choice of optimal first and second line therapies depends upon the classification of the PTLD, the cell of origin (i.e. B- *versus* T-/NK-cell), and presence or absence of EBV [1,51,57-61]. In addition, RIS and DLI both carry the risk of inducing GvHD and multiagent chemotherapy is typically not toleraled early after allo-HCT. In addition to causing organ toxicity 2, this non-targeted approach impairs the stem cell graft and any EBV directed T cells. Adoptive therapy with EBV-specific T cells has been available at only a few transplant centers.

Anti CD 20 monoclonal antibody therapy

For most patients with B-cell PTLD, anti-CD20 monoclonal antibody, rituximab, is appropriate first line therapy. It is effective in approximately 70% of patients and has limited toxicity. The latter include infusion-associated reactions, transient neutropenia and hypogammaglobulinemia. These can mitigated respectively by subcutaneous administration and use of pre-medications; Granulocyte Colony Stimulating Growth Factors (G-CSF); and immunoglobulin replacement therapy [62].

Rituximab treatment strategies

Four different rituximab treatment strategies have been used to minimize PTLD-associated mortality: (1) Prophylaxis (i.e. rituximab is given early post-HCT to all patients); [12] (2) Preemptive therapy: Therapy such as rituximab is administered when EBV viral load exceeds a pre-determined institutional threshold (ranges widely >500 to 100,000/mL); [34,57,63-66] (3) Empiric therapy (i.e. treatment is iniatated when presumed, PTLD is diagnosed based on clinical signs/symptoms and/or imaging and EBV viremia (without waiting for pathologic confirmation by biopsy) in the setting of EBV viral monitoring by PCR [34,63]; and (4) Conventional therapy of established PTLD (i.e. therapy is initiated after the diagnosis of PTLD is established by biopsy). Table 4 summarizes the published results from studies using these four approaches. Our ability to compare these strategies is limited, as most reports are single-center, single-arm, retrospective studies. There have been only four 2-arm retrospective studies (comparing two of the four strategies) [64-67]. None of the strategies has been studied in a prospective, randomized trial. Furthermore, the studies listed in (Table 4) used different endpoints. These drawbacks, together with different HCT settings (e.g., indication for HCT, disease stage, GVHD prophylaxis), further limit the comparability of strategies. It is important to recognize that EBV viral reactivation is not a relevant cliinical endpoint: in a recent

Table 5: Adoptive cellular immunotherapy for PTLD reporting >10 patients.

Author	Study Type	N	Intervention	Outcomes
• Rooney 78	• Prospective Study: 1. Prophylaxis in 39 2. Treatment in 2	39	• Donor-derived EBV-specific T lymphocytes after T cell depleted allo-HCT • 2-4 infusions: 1 x 10^7/kg to 5 x 10^7/kg	• 0/39 (including 6 with high EBV DNA titer) developed PTLD *vs.* 7/61 (11.5%) in control • 2/2 with PTLD had CR to EBV-specific CTLs
• Heslop 77	• Prospective Study: 1. No prior therapy for EBV- positive PTLD 2. Prophylaxis and treatment study	114	• Donor-derived EBV-specific CTL 1. 101 treated prophylactically, including 90 after T cell depleted allo- HCT 2. 13 treated therapeuticaly	• 2/13 died of PTLD • 11/13 had CR • 0/114 at high risk for PTLD developed PTLD after receiving EBV- specific CTL • 5-year OS: 69% (95% CI 60-77%) • 10-year OS: 67% (95% CI 57-76%)
• Doubrovina 75	• Retrospective Study 1. Failed previous therapy or first-line 2. 21 (47%) received prior RTX 3. 35 (73%) on no immunosuppression • Treatment Study	49	• DLI (n=30) • EBV- specific CTL (donor-derived or 3rd party) (n=19) • Included 3 DLI followed by EBV-specific CTLs, and 2 EBV- specific CTLs followed by DLI	• DLI: 1. 17/30 had CR 2. 1/30 PR 3. CR/PR in 73% • EBV- specific CTL: 1. 13/19 (68%) had CR. • Cumulative incidence of EBV-specific mortality at 12 months: 1. 24% with DLI 2. 21% with EBV- specific CTL
• Prockop 92	• Prospective Study: 1. 55 had EBV-positive PTLD 2. 2 had viremia 3. 46/57 had failed prior RTX. • Treatment Study	57	• EBV-CTLs derived from unrelated third-party donors (13 on protocol 95-024 and 18 on protocol 11-130) or primary stem cell donors (26 on 95-024). • Patients received up to 5 infusions of EBV- specific CTLs 1. 1-2 x 10^6/kg/infusion; (18 on protocol 11-130 and 39 on protocol 92-024	• 3rd party EBV CTLs: 1. ORR 67% (9+3/18) • Donor-derived EBV-specific CTLs: 1. ORR= 62% (24/39). 1-yr OS of 72% and 1-year PFS of 67% for 3rd party EBV-CTL. • RTX-refractory subset: 1. 1-yr OS: 50% in 3rd party 2. 1-yr OS: 49% in donor-derived
• Haque 128	• Phase II Study 1. Failed prior conventional therapy or RIS	33	• Third party EBV-CTL	• PR/CR in 64% at 5 weeks and 52% at 6 months • CR in 14/33, and PR in 3/33
• Jiang 126	• Prospective Study 1. Treatment Study	66	• DLI: 52 • EBV-specific CTLs: 14	• 95% response rates

*Patient data included in Doubrovina study [57].

CR: Complete Response; DLI: Donor Leukocyte Infusion; EBNA: EBV Nuclear Antigen; EBV: Epstein-Barr Virus; EBV-CTLs: EBV-Specific Cytotoxic T Lymphocytes; NR: No Response; PD: Progressive Disease; PR: Partial Response; PTLD: Post-Transplant Lymphoproliferative Disorder; RTX: Rituximab; RIS: Reduction of Immunosuppression; OS: Overall Survival; PFS: Progression Free Survival

study by Kalra et al, [57] of approximately 80% of HCT patients who developed EBV viremia post-HCT, only 1% died of PTLD. Similarly, it is problematic to use the development of PTLD as an endpoint in retrospective studies because the trigger to start therapy and the case definitions vary across studies with some but not all requiring a biopsy. In addition, PTLD is a frequent incidental finding on autopsy in patients whose apparent cause of death was not PTLD-related [59]. Thus, more research is needed in this field to provide clear recommentation. However, for patients at high-risk of developing PTLD, a premptive or even a prophylactic (with less evidence) strategy seems appropriate.64

Pre-emptive rituximab therapy

An unresolved issue of preemptive therapy is the EBV viral load threshold at which preemptive therapy should be initiated [61-67]. The recently standardized international unit measurement system should improve this in the coming years.

Thresholds triggering therapy have varied with some centers using thresholds of 1,000 copies/mL [40,68] 10,000 copies/mL 69,70 and >1,000 copies/105 Periperal Blood Mononuclear Cells (PBMC) [56]. However, this is still controversial as recent publications do not uniformly find an association between viral load and development of EBV PTLD [69-71]. Alternatively combining viral load thresholds with CD20 lymphocyte numbers Faraci et al., [6] identified a concentration of 20,000 EBV copies per 105 PBMC with an increase of CD20+ lymphocytes as portending a high-risk of developing PTLD. Similarly, Annels et al, [72] demonstrated that combining analysis of T cell reconstitution at the time of EBV reactivation can help identify patients in need of preemptive therapy. In order to minimize the number of patients exposed to the toxicities of rituximab unnecessarily, few transplant centers favor a relatively high threshold (eg, 300,000 copies /105) before initiating therapy with rituximab [55,73].

Although one dose of rituximab can effectively reduce EBV DNA copy number to undetectable levels, sometimes weekly administration of rituximab for up to four weeks may be required. Concurrent reduction of immunouppression (in an attempt to restore T-cell control over EBV-mediated B cell proliferation) is not effective as the only therapy for EBV PTLD arising after HCT (different from the SOT setting) but when combined with rituximab appears superior to rituximab alone [40,73].

Empiric and conventional rituximab therapy

Treatment of established EBV PTLD with single agent rituximab or rituximab combined with reduction in immune suppression is associated with a response rate of 50-70%. Risk factors for poor response to ritxumab therapy have been established and include: age >50 years, having GvHD at the time of diagnosis, and the presence of CNS disease [1,2].

Conventional Chemotherapy

For CD20 negative PTLD and Classic Hodgkins lymphoma (WHO class 6) rituximab is not appropriate first line therapy and treatment decisions should be driven by histology. In these settings conventional chemotherapy can produce response rates of 70-80%. In general patients with PTLD arising after HCT tolerate chemotherapy poorly requiring frequent dose reduction and dose delays [2].

DLI and EBV-Specific Cytotoxic T Cell (CTL)s

Allo-HCT recipients are poor candidates for multi-agent cytotoxic chemotherapy and often require frequent dose-reductions and administration delays. Thus, cellular therapy that can restore EBV-specific T cell immunity is a viable alternative. In 1994, Popadopolus, et al, [74] first demonstrated that nonspecific donor lymphocytes obtained from HCT donors could irradicate EBV-positive lymphoma that developed after allo-HCT. However, this therapy was associated with a high risk of precipitating GVHD. This group went on to report that 30 patients treated with DLI for EBV-positive PTLD had an overall response rate of 70% and that 14% of these patients developed GVHD [75].

Subsequently, approaches for selection and expansion of EBV-specific T- cells have been developed [76]. Adoptive transfer of these viral specific T-cell populations has been associated with demonstrated efficacy in prophylaxis as well as treatment of EBV viremia and PTLD [77,78]. Table 5 summarizes the results of studies reporting at least 10 subjects receiving adoptive cellular immunotherapy for PTLD [75,77,92,126,128,129]. Vital to the success of this strategy has been the establishment of methods for *in vitro* enrichment of viral-specific T cells with depletion of alloreactive T cells. Initial experience of treating allo-HCT recipients using EBV-specific CTLs generated from the primary HCT donor was encouraging, but limitations of this approach included: (1) difficulty in generating EBV-specific CTLs from seronegative donors or from UCB; (2) the lengthy ex vivo culture process employed in the original studies (approximately eight to ten weeks), [79] and (3) the observation that, in the HLA disparate allo-HCT setting, EBV-specific CTLs of donor origin could be restricted through an HLA allele not shared by the recipient and thus not presented by on PTLD cells of recipient origin.

More recently, investigators have established more rapid production methods including 1) isolation of virus specific T-cells from donor leukocyte collections on the basis of their binding to viral peptide/HLA tetramers or to dissociable streptomers, or 2) on expression of activation markers or cytokines after short-term *in- vitro* sensitization [80-85]. In addition, investigators have genetically modified EBV-specific T cells to make them resistant to the calcineurin inhibitor tacrolimus [86]. These calcineurin inhibitor-resistant T-cells have demonstrated efficacy in pre-clinical models, and a multi-center trial of modified autologous EBV-specific CTL therapy is in development (ClinicalTrials.gov Identifier: NCT03131934) Expanding adoptive EBV-specific T-cell therapy to recipients for whom a donor- derived T cell line is not available has been a major advance in the broader application of this therapy. 86 The first demonstration that "third party" viral specific T cells could be used safely and effectively came in response to limitations in generating autologous EBV- specific T cells. These limitations led investigators to use HLA partially matched EBV-specific T cells derived from a bank of 70 cell lines generated from healthy EBV-seropositive volunteer blood donors to treat 31 SOT and 2 HCT recipients with EBV- positive PTLD [87]. In this study, 52% of patients achieved a Complete Remission (CR) or Partical Remission (PR) that was sustained for > 6 months. Subsequent to this proof of concept study, several groups have demonstrated efficacy in treating allo-HCT recipients with third party banked EBV-specific CTLs. Recently summarized results report on fewer than 200 HCT and SOT recipients treated with EBV- specific T cells, but they confirm the potential efficacy and limited risk of toxicities including GvHD [86,87]. Consequently, many centers have established banks of viral specific CTLs, and multi-center trials are now underway [88-93].

In summary, in the absence of randomized trials, the timing and choice of first and second line therapy varies based on institutional preferences. Rituximab as monotherapy is highly effective except in classical Hodgkin lymphoma and CD20 negative DLBCL. Across studies, clinical efficacy and an absence of toxicity have demonstrated in -vivo successful enrichment of T-cell EBV specificity and depletion of allo-reactivity. CTLs are expected to be widely accessible in future.

T-Cell PTLD: While most cases of PTLD arise from B cells, T-cell- or Natural Killer (NK)-cell PTLD constitute a rare entity following HCT. T-LGL PTLD should also be differentiated from clonal LGL proliferation, which is common following HCT and resolves spontaneously without treatment. In the SOT setting T-NK cell PTLD represent a heterogeneous group of lymphoid disorders that comprise about 10-15% of all PTLD cases [94]. Swedlow and co-workers reported one of the largest case series that included 130 T/NK-cell PTLD and included peripheral T-cell lymphoma NOS and Hepatosplenic T Cell (commonly gamma-delta) Lymphoma (HS-TCL) [94]. Among the rare non-B-cell cases of lymphoma seen in the immunosuppressed patients, the gamma-delta phenotype has been infrequently reported [95,96]. Approximately, two-thirds T-cell PTLD cases are EBV negative and may be associated with, but not caused by other viruses.

Most cases of T-cell PTLD are extranodal and generally more aggressive than B-cell PTLD, with median survival of only 6 months. Favorable outcomes are associated with Large Granular Lymphocytic Leukemia (PTLD-LGL) subtype, younger age and combination therapy of chemotherapy and radiation. Patients with EBV negative T-cell PTLDs had significantly shorter overall survival (median 6 months *versus* 18 months; p= 0.0347). Other adverse factors are advanced stage, bone marrow graft, CNS or graft involvement, and HS-TCL type. 12 Unlike PTLD of B-cell origin, rituximab, the most effective and tolerable agent used to treat B-cell PTLDs, has no role in T cell PTLD because these cells do not express CD20. Conversely, treatment of T-cell PTLD consists of RIS with or without conventional chemotherapy. Recently, case reports suggest a role for novel therapies including brentuximab [97]. Alternative treatment

Table 6: Reported Incidence of EBV- Positive PTLDs following Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HCT).

Study	Patients	Incidence	EBV status	EBV- negative PTLD
Lan-Ping 2015 [129]	45	3% in Haploidentical HCT	Positive	Excluded histologic EBV-negative and EBV DNA- negative patients
Hale 1998 [26]	20	1.3% PTLD with campath	Positive	No information re:EBV-negative PTLD
Gerristen 1996 [130]	65	14% PTLD with campath	Positive	No information re:EBV-negative PTLD

strategies include use of agents to induce the lytic phase of EBV gene expression in tumor cells and may sensitize these cells to the anti-viral agent, gancyclovir. Among these agents are histone deacetylase inhibitors, such as arginine butyrate, valproic acid, and panobinostat [98].

In summary, there is no role for conventional B cell targeting PTLD treatment in T-cell PTLD. Clinical trials with brentuximab, alemtuzumab and EBV-specific cytotoxic T-cells are ongoing.

EBV-Negative PTLD: While exact incidence is unknown, the reported incidence of EBV-negative PTLD varies, ranging from approximately 1 to 34% [99-102]. As EBV negative PTLD is more common after SOT much of our understanding of this entity is extrapolated from that setting. Some reports recognize EBV-negative PTLD as a distinct entity, citing its late occurrence, frequency of hodgkins and monomorphic histologies (including diffuse large B cell lymphoma) and distinct genomic profile [103,104]. In SOT recipients, the risk factors of advanced stage, older age, high LDH and CNS involvement comparable in EBV negative and EBV-positive PTLD [105]. One hypothesis is that EBV-negative PTLD may, in fact, had been EBV-positive but over time lost its "EBV foot print". This hypothesis is supported by the observation that EBV-negative PTLD is associated with late occurrence post-HCT. Other possible explanations for EBV negativity include lymphoid stimulation from yet an unidentified virus or other infection. It appears that EBV-negative PTLD has become more prevalent although the actual incidence may not be rising. In the past, EBV positivity was considered pathognomonic for a diagnosis of PTLD, and thus EBV-negative PTLD patients were excluded from the diagnosis. Table 6 illustrates this point: in these studies, either EBV positivity versus negativity was not reported for allo-HCT patients whose PTLD was EBV-negative or patients who did not have EBV virus detected in the blood were excluded. It should be noted that in the SOT setting, the response to reduction in immunosuppression is similar for EBV-positive and EBV-negative patients.

In summary, EBV positive or negative status does not preclude diagnosis of PTLD as 10-20% patients with PTLD have EBV negative PTLD. Clinical prersentation, response to reduction in immunosuppression reduction, rituximab and prognosis is similar for EBV postive and EBV negative PTLD. Patients with EBV negative PTLD are however not candidates for EBV directed adoptive immunotherapy.

Ptld Following Sot *versus* Hct

The clinical signs, symptoms, and diagnostic evaluations are similar for PTLD following SOT and allo-HCT [2]. Based on intensity and duration of immunosuppression, the highest incidence occurs in haploidentical HCT, heart/lung and multivisceral transplants [106,107]. The Scientific Registry of Transplant Recipients reports 5-year-incidence of EBV-positive PTLD in intestinal transplants (~9%), followed by lung/pancreas (~2%), liver/heart (~1%), and kidney (~0.5%) transplant recipients [2]. In a large CIBMTR report of related and unrelated allo-HCT, the cumulative incidence of PTLD was low at 0.2% among patients with no major risk factors, but increased to 8% in high risk patients [37].

Table 7: Differences between PTLD following Allo-SCT and SOT [15].

PTLD characteristics	Allo-SCT	SOT
Incidence	0-2%	0-33%
Median time to onset	6 months	36 months
Graft involvement by PTLD	Rare	Common
Spleen involvement by PTLD	Common	Rare
PTLD cellular origin	Mostly donor	Mostly recipient

The most common location of PTLD is in the lymph nodes, but, for SOT recipients of lymphocyte rich tissues such as lung or liver there is an overrepresentation of PTLD within the graft [103-107]. Furthermore, PTLD involvement of the spleen is more common in PTLD arising after allo-HCT compared to that arising after SOT [108,109]. Median time to PTLD for allo-HCT recipients is 6 months compared to 36 months in SOT recipients [108]. PTLD can be both of recipient and donor cell origin; in allo-HCT, donor origin is more frequent whereas recipient origin is more frequently seen in SOT. In general, the long-term overall survival after allo-HCT PTLD is poor (below 50%) with a slightly better prognosis in SOT patients [109]. Fortunately, the incidence of PTLD has been decreasing in recent years, especially in SOT recipients, a reflection of modern immunosuppression [110].

In summary, compared to HCT associated PTLD, SOT related PTLD occurs with higher frequency, long latency, derives from recipient organ and may involve graft itself (Table 7) [15,108-110].

Prognosis and Future considerations

In the rituximab era, the three-year survival from PTLD arising after allo-HCT is approximately 70% [1,2,111]. Patients whose disease fails to respond to or relapses after rituximab therapy, however, have a dismal prognosis. The considerable advances in our understanding of PTLD as related to classification, diagnosis and preemptive treatment with anti-CD20 antibody have improved outcomes. On the other hand, areas that warrant further investigation include better identification of allo-HCT recipients who would benefit most from prophylactic or preemptive therapy. Genomic studies identifying different PTLD subtypes may lead to more precise classification and treatment strategies. Improvements in imaging, tighter correlations between EBV viral load and risk of developing PTLD, and the development of treatment modalities that are relatively non-toxic, affordable, and accessible likely will contribute to enhancing survival. Finally, attention needs to focus on recognizing the EBV- negative and the non-B cell PTLD subtypes. For example, for PTLD cases that express CD30, the anti-CD30 antibody, brentuximab vedotin,

may be an attractive treatment strategy and is the subject of ongoing studies. Tabelecleucel (allogeneic EBV-specific cytotoxic T cells) administered at doses of 2 x 106 cells/kg on days 1, 8 and 15, followed by observation through day 35 is being investigated in multicenter trials [112]. Similarly, an ongoing phase I study combines nivolumab with autologous EBV-specific T cells holds promise [113-130]. While fever than 300 allo-HCT recipients have received EBV directed CTLs the safety profile and efficacy to date is promising and will be expanded by ongoing trials.

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