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Joining efforts for PTLD: lessons learned from comparing the approach and treatment strategies across the pediatric and adult age spectra

Francesca Montanari, MD,

Department of Hematology, Yale Cancer Center, Smilow Cancer Hospital

Manuela Orjuela-Grimm, MD, ScM

Division of Pediatric Hematology, Oncology, and Stem Cell Transplant, Departments of Pediatrics and Epidemiology, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center

Structured abstract:

Purpose of review: Post transplant lymphoproliferative disorders are a rare and heterogeneous group of diseases, where large prospective studies have been difficult to perform and treatment paradigms are often based on retrospective studies. Here, we critically analyze and present the clinical algorithms commonly used for this disease, with a special focus on the challenges and differences of the approaches in the adult and pediatric populations.

Recent findings: Clinical trials exploring combinations of immunochemotherapies with a sequential and risk stratified strategy have demonstrated exciting results, but are hampered from specialty and age determined silos. Approaches introducing novel targeted therapies and cellular therapies are currently being explored with a goal of joining efforts across the pediatric and adult age spectra.

Summary:

We propose that future therapeutic approaches would benefit from combining pediatric and adult PTLD efforts, gaining from the experience garnered from the age and subtype specific tailored strategies, with the aim of limiting treatment related toxicities while maximizing the efficacy.

Corresponding author: Manuela Orjuela-Grimm MD ScM Mailman School of Public Health 722 West 168th street, Room 730 New York, NY 10032 Mao5@cumc.columbia.edu.

Compliance with Ethical Standards

Conflict of Interest

Dr Francesca Montanari has received research funding from Seattle Genetics

Dr Manuela Orjuela has been a scientific advisor for Atara biopharmaceuticals.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Joining of efforts holds enormous potential for accelerating access to novel therapeutic strategies for PTLD in the near future.

Keywords

post-transplant lymphoproliferative disorders (PTLD); rituximab; brentuximab vedotin; immunochemotherapy; immunosuppression reduction; adoptive T cell therapy; adults; pediatrics

Introduction

Post-Transplant Lymphoproliferative Disorders (PTLD) are defined by the revised 2017 edition of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues as "lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ, bone marrow or stem cell allograft" [1]. Within this definition 4 distinct categories exist, including: (1) Non-destructive PTLDs (plasmacytic hyperplasia, infectious mononucleosis, and florid follicular hyperplasia), (2) Polymorphic PTLD, (3) Monomorphic PTLD, and (4) Classical Hodgkin Lymphoma (HL) type PTLD. As non-destructive PTLD do not meet the definition of malignancy, the topic of this review will focus on polymorphic, monomorphic and classical HL type PTLD.

The incidence of PTLD varies between different transplanted organs and by pediatric and adult groups. Recent published data from the US Organ Procurement Transplant Network & United Network for Organ Sharing (UNOS) database have established the 10-year risk of PTLD in Adult Renal Transplantation at 0.7%, Liver Transplantation 1%, Heart Transplantation 1%, Pancreas Transplantation 1% and Lung Transplantation 2% [2, 3]. The 10-year risk of PTLD in recipients of allogeneic hematopoietic stem cell transplants as calculated by the International Bone Marrow Transplant Registry (IBMTR) and the Fred Hutchison Cancer Research Center is 1% [2]. In the only population based study of incidence of PTLD, incidence was found to be 159/100,000 person years post solid organ transplant, with EBV present in slightly over half of all PTLD [4].

Across all transplants, monomorphic PTLD is the most common accounting for 75% of all cases. Lymphoma derived of B cell origin account for the majority of cases (70%), while T-cell neoplasms represent a small minority (5%). Within monomorphic PTLD, 50% of cases demonstrate association with the Epstein Barr Virus (EBV). Polymorphic PTLD accounts for 15–20% of all PTLD cases in adults with the majority demonstrating EBV involvement, while in pediatrics the proportion with EBV is variable and likely reflects other factors including time since transplant (see below) [4]. Classic HL type PTLD are generally associated with EBV though EBV negative cases have also been reported [5, 6]. Other viruses such as CMV, HHV8, Hepatitis C [4] have also been detected in PTLD, though their role in disease initiation or progression is poorly understood [7].

Currently our understanding of the pathogenesis of PTLD is incomplete. Despite concerted efforts we are unable to predict who will develop PTLD, and we do not understand why only 1–2% of all transplant recipients develop these disorders. Two different mechanisms appear to be at play in the development of PTLD at different time points post transplantation; those

considered early (<1-year post transplant) and those considered late (>1-year post transplant).

Early PTLD occurs more frequently in allogeneic hematopoietic stem cell transplantation than in adult solid organ transplantation [2]. The significant risk factors for developing early PTLD in adults are recipient EBV sero negativity, acute EBV infection/reactivation, T cell depletion (particular with anti-CD3 monoclonal antibodies or anti thymocyte globulin) and HLA mismatching [2]. In a study of tissue that were assessable for EBV related sequences in the IBMTR / Fred Hutchinson Cancer Center Registry, all early PTLD cases demonstrated EBV related sequences, whereas this finding was not evident in late-onset PTLD [2]. The major risk factors for **late**-onset PTLD are age and ongoing immunosuppression, particularly with calcineurin inhibitors [8].

In pediatric oncology populations (through age 21 years in the US), PTLD is more frequent after solid organ transplants (SOT). In contrast to bone marrow transplant settings where PTLD originates in donor cells, in SOT, PTLD arises overwhelmingly in host cells. The treatment strategies between the two forms differ in large part related to this difference. The remainder of our pediatric discussion focuses on that occurring after SOT. The risk for PTLD differs substantially depending on the degree of immune suppression required for graft maintenance. Heart and small bowel transplant pediatric patients have higher risk with more than 5% of transplants developing PTLD, while the rates are lower in liver and kidney transplant patients who can often be weaned off immune suppression. The type of immunosuppression after SOT appears to influence risk of developing PTLD [9]. Many pediatric patients receive their SOT prior to exposure to EBV and tend to be seronegative at time of transplant. In pediatric PTLD, most early PTLD (variable definitions in pediatrics, but generally within 18 months after SOT) are EBV positive, while late onset PTLD in pediatrics is much more likely to be EBV negative [10, 11].

The diagnostic work up in pediatrics is heavily influenced by the distribution of morphologies that can present in pediatric PTLD including the relatively higher prevalence of burkitt's morphology and of CNS involvement and which require different therapeutic approaches, (see below). Therefore the standard of care in pediatric oncology is that pediatric patients with biopsy-proven PTLD undergo a diagnostic work up that includes bilateral bone marrow biopsies and lumbar puncture, in addition to radiologic imaging (with PET-CT). Therapeutic considerations are also increasingly impacted by molecular documentation of clonal populations with VDJ (and TCR) rearrangements which permit following clonal subpopulations and determining if recurrent disease represents new or returning populations. A subgroup of pediatric patients present with a sepsis like presentation with multisystem organ failure. This presentation is referred to as Fulminant-PTLD or F-PTLD. In such patients diagnosis is often limited by clinical conditions and often involves only bedside procedures. [23] In adults, following the pathological diagnosis of PTLD, staging is routinely performed by PET-CT. However, in contrast to pediatric practice, bone marrow evaluation is reserved for patients presenting with clinical stage I to rule out systemic involvement of disease, when local modalities of therapy, such as surgical resection or radiation therapy, are considered. Lumbar puncture evaluation is reserved to patients with neurological symptoms or deemed high risk for CNS involvement based on criteria

extrapolated from risk scoring for diffuse large b cell lymphoma in immunocompetent patients.

With regards to prognosis, a large series of 45 pediatric patients treated in a single institution demonstrated CD20 expression in tumors had significantly improved 5-year event free (regardless of rituximab usage), and overall survival (96% vs. 56%). early onset PTLD also had better survival compared with late onset PTLD. In contrast, EBV status did not affect survival, though early onset PTLD were after SOT) [11]. Similarly, in one of the largest series of PTLD (including some patients reported in the pediatric article above) from a single institution, CD expression along with age and performance status were the most important variables in predicting outcome. Using a recursive prognostic partitioning model, four risk groups were identified: (1) low-risk (median overall survival (OS) not reached), (2) intermediate-low-risk (median OS 6.8 years), (3) intermediate-high-risk (median OS 1.8 years) and (4) high-risk (median OS 1.3 months). Beyond age, the key differences between the pediatric and adult populations were, increased frequency of early lesions in pediatric patients and more frequent extra nodal involvement in adult patients. These differences along with the EBV status which was similar in the two groups did not impact survival [12].

Table 1 summarizes key SOT characteristics, aspects of clinical presentation, relative frequency of histologic subtypes, and diagnostic work up which inform the therapeutic approaches for treating pediatric and adult patients with PTLD.

Current therapy strategies for PTLD

PTLD are rare and heterogeneous diseases where large prospective trials have been difficult to perform. Most of our knowledge on PTLD treatment is based on retrospective studies. The current cornerstones of the management of PTLD are reduction of immunosuppression (RIS), CD20 monoclonal antibody therapy with rituximab, conventional chemotherapy and adoptive T-cell therapy. Surgical extirpations of disease and localized radiation therapy have a very limited role, in isolated cases of disease or for palliation. The aim of initial therapy is to achieve complete remission (CR) while attempting to minimize adverse effects given the significant pre-existing co-morbidities that led to the necessity of a transplant and those arising from chronic immunosuppression and infectious complications. Common challenges in the care of these patients are related to the high frequency of decreased renal function at baseline, due to immunosuppressive therapy, and potential impairment of the transplanted organ, due to PTLD involvement, rejection episodes, age of the graft. Infectious complications and sepsis are common in this population and the main cause of the elevated treatment mortality, reported as high as 31% in the adult population receiving standard immunochemotherapy [7][18]. Partial responses should not be viewed as a successful outcome, given that these are not robust and ongoing therapy in this immune-compromised population is associated with significant morbidity and mortality.

- **Reduction of immunosuppression—**The primary goal of a reduction in immunosuppression is to re-establish host T cell function to control lympho-proliferation. However, this may come at the cost of transplant organ rejection. As a sole therapeutic strategy, RIS demonstrated 6% partial response rate with no complete responses in patients

who undergo immunosuppression reduction in the only prospective study conducted evaluating this strategy. Of note, this 16-patient trial had a rate of graft rejection of 38% [13]. Therefore, reduction of immunosuppression is usually implemented during the initial work up and combined with other treatment modalities. Typically, reduction of calcineurin inhibitors by at least 50% and discontinuation of antimetabolic agents is performed. Factors predictive of poor response to RIS in adult patients are typically EBV negative disease, bulky disease, advanced stage, and older age [14]. In pediatric SOT patients, poor predictors for response to decreased immune suppression alone include CD20 or EBV negativity and late onset PTLD, as well as those with CNS involvement or with Burkitt's or Hodgkin's morphology [10, 11].

- **Rituximab—**Rituximab is a chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. The CD20 antigen is found on pre-B and mature B-cell lymphocytes but not haematopoietic stem cells, pro-B cells or other normal tissues. The Fab domain of Rituximab binds to the CD20 antigen and the Fc domain recruits immune effector functions to mediate B cell lysis in vitro. Mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). Rituximab has been an integral part of therapy in B-cell NHL for over 15 years. In the setting of PTLD, it has been studied extensively as a single agent and is an integral part of the sequential therapy protocol of the PTLD-1 trial. To date, there have been 3 prospective trials of Rituximab monotherapy in PTLD. Two trials examined the use of 4 weekly doses of Rituximab alone while another study performed by GEL/TAMO & GELCAB utilized 4 weekly doses of Rituximab followed by additional 4 weekly doses in patients who had achieved only a partial response [15–17]. Combined analysis of the Oertel SH et al. and Choquet S et al studies demonstrated a complete response rate to 4 weekly doses of single agent Rituximab of 42%, partial response rate of 17% and progressive disease and stable disease in 41% of patients. Remissions achieved were not durable, with 26% of complete and partial responders requiring further therapy within 1 year [18]. The use of a second cycle of Rituximab therapy as per the GEL/TAMO & GELCAB study improved complete response rates to 61% converting most partial responses to complete responses [17]. However, as with the other studies, remissions were not durable with an event free survival of 42% at 27.5 months.

- **Immunochemotherapy strategies—**Historically, transplant recipients tolerate conventional chemotherapy poorly. A treatment related mortality (TRM) of up to 31% has been reported utilizing cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for PTLD [16, 18]. This is contrast to the TRM of 2% in a study of over 1000 patients with Diffuse Large B cell Lymphoma receiving Rituximab CHOP [19]. Despite this toxicity, patients able to tolerate conventional chemotherapy can achieve long lasting remissions from PTLD.

The PTLD-1 trial, a large multi-center prospective study in these disorders, established a role for sequential therapy [20]. Primarily conducted in central Europe, this phase II study incorporated 4 weekly doses of Rituximab monotherapy followed by 4 cycles of CHOP. Twenty percent of patients achieved a CR following Rituximab monotherapy which

increased to 57% following the completion of sequential therapy. The median progression-free survival (PFS) was 4 years with a median overall survival (OS) of 6.6 years. Of significance, the TRM of sequential based therapy remained high at 11% but lower when compared to historical controls. A potential reason for this is that initial pre-phase rituximab monotherapy leads to a lower tumor mass and improved performance status at the time of CHOP therapy. Response to Rituximab induction in this study was a prognostic factor for OS [20].

In the subsequent study by the same group (PTLD-2 trial), the largest prospective trial ever conducted in PTLD patients, a risk stratification approach was implemented in the sequential therapy strategy. Patients achieving a CR after rituximab induction (low-risk) were treated with rituximab consolidation alone, whereas therapy was escalated to RCHOP in non-complete responders (high-risk group). Seventy percent of the patients achieved a CR, with a 3-year time to progression in the low-risk group of 89%, suggesting that achieving a CR after immunotherapy induction identifies a group of patients, although small (25%), that does not need cytotoxic chemotherapy. TRM was 8% and median OS 6.6 years. The results of this trial established this therapy strategy as standard of care in Europe [21].

In the US, a retrospective review compared results of R-CHOP with R-EPOCH in adult patients with monomorphic PTLD, DLBCL subtype, diagnosed and treated at Columbia University medical center, comparing, patients treated with R-CHOP (N=9) with clinically similar patients (N=25) treated with R-EPOCH (the same agents as in RCHOP, with the addition of etoposide and administration of etoposide, vincristine, doxorubicin as a continuous infusion In this study, the complete response rate for R-CHOP was 66.6% compared with 84% for R-EPOCH though the difference was not significantly different ($p= 0.27$) and neither toxicity nor EFS nor OS differed between the groups [22]. The limited number of patients treated with R-CHOP limited the statistical comparison. Additionally, patients treated with RCHOP were twice as likely to have refractory disease prior to starting RCHOP therapy compared with those treated with REPOCH [22].

For pediatric PTLD, combined immunochemotherapy began by building on a moderate dose cyclophosphamide and prednisone 21 day cycle therapy and adding 6 weekly doses of Rituximab with the first two cycles. This initial study at Columbia University [23] served as a pilot for a national cooperative group phase 2 trial (ANHL 0221) in the Children's Oncology Group (COG) demonstrating the feasibility of treating PTLD in a pediatric cooperative group in the US. The COG study showed a 2-year EFS of 77%, and OS of 80% [24]. Importantly, this is the only regimen reported to be effective in F-PTLD in pediatrics which prior to this therapy was considered uniformly fatal. Since that study, there have been additional cooperative group trials in both the US and Europe, most notably Peds PTLD 2005 in central Europe, which obtained a similar response rate but gave up front rituximab monotherapy (3 weekly doses and then 3 additional doses at 21 day intervals), giving additional chemo (cyclophosphamide, vincristine, methotrexate-at moderately low dose, prednisone) only when progressive disease occurs with rituximab monotherapy [25–27]. With this approach approximately half of patients are able to avoid cytotoxic chemotherapy.

Distinct subtypes of PTLDs requiring different approaches

The immunochemotherapy strategies summarized above, and in particular the sequential, risk stratified approaches, have been investigated in polymorphic and monomorphic B cell PTLD with an overwhelming predominance of DLBCL like PTLD. The less common subtypes of PTLD, such as monomorphic PTLD Burkitt's type, plasmablastic type, of T cell monomorphic, HL PTLD and PTLD with central nervous system (CNS) involvement, are usually managed similarly to lymphomas developed in their immunocompetent counterparts, though with special challenges deriving from impaired organ function due to long standing use of calcineurin inhibitors, concern for graft function, , and concern for potential iatrogenic toxicity, as well as the heightened risk for infectious complications. In pediatric settings, the relative frequency of these morphologies appears higher than in adults, and their treatment routinely requires dose reduction of cytotoxic agents.

Burkitt's morphology PTLD will generally have the chromosomal translocations characteristic of non PTLD Burkitt's and share the same aggressive behavior. One of the challenges peculiar to treat this disease is the limitation in the use of certain key drugs, such as methotrexate, due to generally poor renal function reserve in patient receiving immunosuppressive therapy and in renal transplant recipients, compared with their immunocompetent counterparts. Therefore, milder therapy paradigms such as R-EPOCH are utilized in the adult populations and dose reductions of the methotrexate are often applied in the pediatric and adult setting [28].

For Hodgkin's and Hodgkin's-like PTLD in the adult population therapy follows standard protocols. In pediatrics, modifications such as holding involved field radiation if patients achieve a CR after the initial phase of therapy (OEPA) are incorporated in an attempt to decrease toxicity [6]. Response is generally good, though patients appear to have more frequent toxicities than non-PTLD patients receiving the same regimens. PTLD involving the CNS are rare, and prompt initiation of chemotherapy, with the exclusion/omission of RIS implementation being key. Treatment approaches are guided by CD20 and EBV status. In cases where the CNS involvement is present along with systemic /nodal involvement, if tumor cells are CD20 positive, rituximab is given systemically at a higher dose or intrathecally and high dose methotrexate containing regimens at doses somewhat lower than for CNS lymphoma, depending on renal excretion, followed by high dose cytarabine based treatment and then consolidation with EBV cytotoxic T cells (see below) when patients have EBV positive disease [29–32].

New strategies

B-cell PTLD exhibit somewhat inferior outcome in terms of overall survival when compared to other patients with NHL. The 5-year OS in the PTLD-1 trial was 57%, while during a similar time period as this study was conducted (2002–2006), the 5-year survival of patients with NHL in the United States (SEER Database) was 65% [20, 33]. Beyond the excessive treatment-related mortality, a significant factor in this inferior survival is the inability to tolerate therapy due to the increased amount and severity of co-morbidities found in transplant recipients. This observation begs consideration of novel therapeutic combinations

that are able to provide sufficient anti-lymphoma therapy without the deleterious effects of such treatment. Table 1 summarizes currently ongoing clinical trials.

A recent study of 59 B-cell PTLD cases at Columbia University Medical Center has identified that 66% have >20% expression of CD30 [34]. Within this case series 81% of CD20+ PTLD cases expressed CD30. Although CD30 expression (CD30+) was more common in EBV positive cases (32/41 cases), CD30 was expressed in a large portion of the EBV negative cases as well (7/18). Similar findings were reported by Vase at al, in a series of 108 patients, where the immunohistochemical expression of CD30 was consistently detected in all types of PTLD (overall 85.25%), including the monomorphic subtypes, and was correlated with a more favorable outcome [35].

Based on these findings, brentuximab vedotin, an antibody drug conjugate targeting CD30 that received accelerated FDA approval for previously untreated CD30+ T-cell lymphoma and Hodgkin lymphoma, has been investigated in CD30+ PTLD.

In a recent study, Pearse at al reported the results of the combination of brentuximab vedotin plus rituximab, as upfront therapy, in a small series of 22 patients with immunosuppression-associated CD30+ and /or EBV+ lymphomas which included 16 patients with PTLD [36]. The combination had an acceptable safety profile and appeared effective, with over half of the patients achieving a CR. With a median follow up of 26 months, the probability of PFS was 75% at 1 year and 67% at 3 years.

A trial evaluating a sequential risk stratified approach utilizing the combination of brentuximab vedotin with rituximab plus or minus bendamustine is currently ongoing (NCT04138875).

Adoptie T cell therapy

In EBV positive pediatric PTLD, EBV cytotoxic T cells appear to be present at time of diagnosis and increase during treatment with rituximab, as well as during reduced immune suppression, and even when EBV viremia returns at end of therapy, the EBV cytotoxic t cell response appears strong, in some patients [37]. However, there are subgroups of patients whose EBV response is insufficient after rituximab therapy. For those latter patients, EBV Cytotoxic T cell (CTL) therapy is increasingly used as a consolidation. EBV CTL has been used for EBV driven post-transplant lymphoma since 1996 when it was first derived from donor lymphocytes and used in allogeneic stem cell transplant patients [38, 39]. More recent generation of LMP2 targeted third party ‘off the shelf’ CTL’s have been developed for use in rituximab refractory PTLD, demonstrating encouraging response in both allogeneic stem cell transplant populations and in SOT, though the number of SOT patients treated successfully remains small [40]. Until recently, therapy was restricted to academic centers where CTLs could be generated, but recent trials have expanded access to EBV specific cytotoxic T cells in rituximab refractory disease by allowing administration in centers with stem cell transplant abilities. Several trials for the pediatric and adult populations are ongoing including the current COG PTLD trial, and the ATARA Tabeleleucel trial (Table 2). Additional efforts have combined both brentuximab vedotin and third-party CTL’s for rituximab refractory PTLD [41].

Other challenges in treating PTLD include the limited options for therapy in refractory PTLD and the need for exploring alternative therapeutic combinations, particularly for EBV negative disease, which is increasingly realized to comprise a biologically distinct entity [42, 43] [4] and accounts for nearly half of all cases, as well as for PTLD involving the CNS.

Conclusions

Pediatric and adult approaches to management of PTLD share important strategies for both diagnosis and therapy, but the differences in approach may also inform both fields and offer opportunities for synergy in some subgroups. The relative rarity of PTLD subgroups has hampered abilities to include PTLD efficiently in cooperative group trials. Some subgroups of pediatric PTLD overlap with the more common adult PTLD types and could be treated in the context of a combined adult-peds or peds/AYA trial. Furthermore, international consortia are more likely to facilitate more timely progress in phase 2 trials and to enable the capacity for phase 3 trials. Future abilities to examine therapeutic options through phase 3 trials will likely benefit from including both life-course groups when appropriate.

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Abbreviations:

PTLD	Post Transplant Lymphoproliferative Disorders
SOT	solid organ transplant
PET CT	positron emission tomography- computerized tomography
RCHOP	rituximab cyclophosphamide, doxorubicin, vincristine and prednisone
R EPOCH	rituximab, cyclophosphamide and prednisone, with continuous infusion of etoposide/ vincristine/doxorubicin

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Table 1:

Differences in patients' characteristics, clinical presentation, histology and diagnòstic work up of pediatric and adult PTLD

	Pediatric	Adult	Relevance
Age at transplant	Bimodal: infancy (for congenital defects, including most commonly congenital heart disease, biliary atresia; ages 10–15 (for viral cardiomyopathy)	Peak incidence of SOT is during the fifth and sixth decade of life	The age at transplant correlates with the pre transplant EBV serologic status of the patient. Recipients of transplant in infancy are less likely to have seroconverted and more likely to be EBV serology negative at the time of transplant. - while later in life is EBV serology positive.
More common clinical presentation	Isolated cervical adenopathy; intussusception, mesenteric adenopathy and bowel wall thickening especially at ileocecal junction.	Extranodal involvement in particular of the gastrointestinal tract, solid allograft and CNS	Although presentation is heterogeneous, extranodal involvement appears more prevalent compared with NHL, and in the adults population it is not rare to have solid allograft involvement
Organ transplanted in order of relative frequency of PTLD requiring oncologic care	Heart or Small intestine/ multivisceral organ transplant > liver > kidney	Heart > Kidney > liver > lung > other SOT and multiorgan transplant	Although the risk of developing PTLD is a function of EBV infection/reactivation and the amount and duration of the immunosuppressive therapy, the total number of each SOT performed in each age group, determines the relative abundance of cases, which differs in pediatric and adult population.
Distribution of Histologic subtypes	DLBCL > Burkitt's lymphoma > plasmacytoid/ plasmablastic > Hodgkin's or Hodgkin's like	Monomorphic B cell type (with predominance of DLBCL) > polymorphic > monomorphic T cell type > Hodgkin like	Histology is the main determinant of the diagnostic work up and therapeutic approach. Differences in the relative frequency of certain high risk subtypes such as Burkitt's lymphoma, lead to differences in the staging procedures.
Diagnostic work up	Pathology inclusive of IHC, EBERish, flow cytometry, cytogenetics and clonality studies. CT (with PO and IV contrast) of neck/ chest/ abdomen/ pelvis and PET/CT (both). MRI of brain depending on clinical presentation Bilateral bone marrow biopsies in all biopsy proven PTLD patients Lumbar puncture without IT chemotherapy in all biopsy proven PTLD patients	Pathology inclusive of IHC, EBERish, flow cytometry, cytogenetics and clonality studies. PET/CT (CT usually without IV contrast especially in kidney transplant recipients) MRI brain and spine: if CNS or leptomeningeal disease suspected Bone marrow biopsy in selected cases (i.e. cytopenias and/or to confirm limited disease) Lumbar puncture with IT chemotherapy of prophylaxis in selected cases (i.e. presence of risk factors)	While pathological evaluation overlaps, in the adult's population bone marrow biopsy is generally unilateral and reserved to cases presenting with cytopenias or to confirm limited stage of disease. Lumbar puncture is usually performed with IT chemotherapy for diagnostic and prophylaxis in patients considered at high risk of CNS involvement based on location of disease or imaging, extrapolating data from the DLBCL counterpart in immune-competent patients.

Table 2:

Clinical trials currently recruiting, exploring novel agents and combinations in PTLD

Agents	PTLD Disease status	Study phase	Trial status	ClinicalTrials.gov Identifier
Brentuximab vedotin + Rituximab	Untreated CD30+ and/or EBV+ CD20+	I/II	Active, not recruiting	NCT04138875
Risk stratified sequential treatment with rituximab+ brentuximab vedotin +/− bendamustine (RBvB)	Untreated CD30+ / CD20+	I/II	Not yet recruiting	
Risk-stratified sequential treatment with Rituximab SC +/− CHOP-21 or Rituximab SC + CHOP-21 alternating with DHAOx (The PTLD-2 Trial)	Untreated	II	Recruiting	NCT02042391
Rituximab + Acalabrutinib	Untreated	II	Not yet recruiting	NCT04337827
Tabelecleucel	rituximab refractory EBV+	III	Recruiting	NCT03392142 * NCT03394365/ NCT02822495
Tacrolimus-resi stant autologous EBV-specific cytotoxic T-cells	*De novo* or resistant to rituximab EBV+	I	Recruiting	NCT03131934
EBV-specific T-cell lines	EBV+	I	Recruiting	NCT02580539
Allogeneic CD30 Chimeric Antigen Receptor Epstein-Barr Virus-Specific T Lymphocytes	CD30+	I	Not yet recruiting	NCT04288726
Rituximab and LMP-Specific T-Cells in Treating Pediatric Solid Organ Recipients With EBV-Positive, CD20-Positive Post-Transplant Lymphoproliferative Disorder (ANHL1522 COG)	Newly diagnosed and relapsed EBV+ pediatric	II	recruiting	NCT02900976 *
VRx-3996 + valganciclovir	Relapsed/refractory EBV+	I/II	Recruiting	NCT03397706

* Includes a pediatric population