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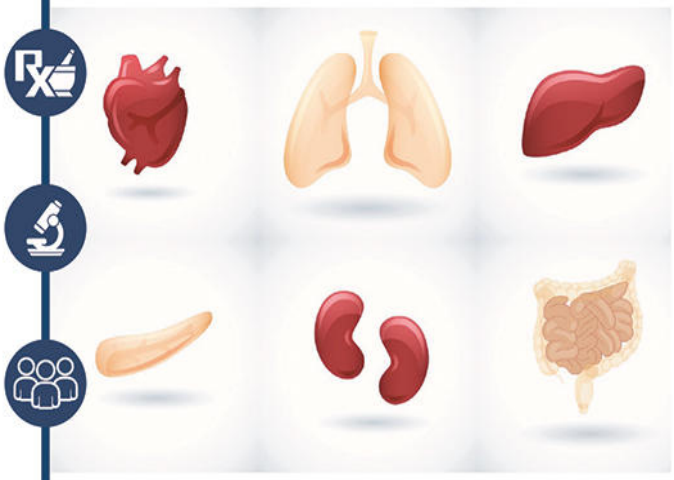

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Post-transplant Lymphoproliferative Disorders, EBV infection and Disease in Solid Organ Transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

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Abstract: These updated guidelines from the American Society of Transplantation Infectious Diseases Community of Practice review the diagnosis, management and prevention of post-transplant lymphoproliferative disorders (PTLD) and other Epstein-Barr virus (EBV) syndromes after solid organ transplantation. PTLD are a heterogeneous spectrum of predominantly B cell disorders, often extra-nodal, with complex distinct pathogeneses and variable clinical presentations determined by pathologic subtype. Recent epidemiologic studies report a decrease in early EBV positive (+) PTLD and an increase in late EBV negative (-) PTLD. Pre-transplant

EBV seronegativity and primary EBV infection, often from donor-transmitted infection, is an important risk factor for EBV syndromes and early EBV+ PTLD. Low quality evidence supports pre-emptive prevention strategies for early EBV+ PTLD in EBV seronegative recipients that involve EBV DNA measurement in peripheral blood using assays requiring further result harmonization, combined with interventions to lower viral load. Reduction in immunosuppression [RIS] is the best validated intervention. WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis; optimal staging procedures are uncertain. Treatment of CD20+ PTLD with the response-dependent sequential use of RIS, rituximab and cytotoxic chemotherapy is recommended. Evidence gaps requiring future research and alternate treatment strategies including immunotherapy are highlighted.

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Key words: Epstein–Barr virus (EBV), lymphoproliferation, PTLD, rituximab, viral infection

Abbreviations: ACVBP chemotherapy, (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone); ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; ATP, adenosine triphosphate; BAL, bronchoalveolar lavage; CHOP, Cyclophosphamide, Hydroxydaunorubicin (also called doxorubicin or Adriamycin), Oncovin (vincristine), Prednisone or prednisolone; CMV, cytomegalovirus; CNS, central nervous system; CT, computerized tomography; CTL, cytotoxic T lymphocyte; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative On- cology Group; HIV, human immunodeficiency virus; IL6, interleukin 6; IVIG, intravenous immune globulin; LDH, lactate dehydrogenase; PET, positron emission tomography; PNCL, primary central nervous system lymphoma; PTLD, posttransplant lymphoproliferative disorder; RSST, risk stratified sequential treatment; SRTR, Scientific Registry of Transplant Recipients.

Introduction

This document summarizes current recommendations and supporting data that guide the prevention, diagnosis and treatment of both EBV-positive (EBV+) and EBV negative (EBV-) post-transplant lymphoproliferative disorders (PTLD) in the solid organ transplant recipient. Although the focus is largely on PTLD, relevant aspects of non-PTLD EBV syndromes are also addressed. Wherever appropriate, recommendations and research priorities are summarized.

PTLD is recognized as one of the most devastating complications of organ transplantation (1-3). The Epstein–Barr virus (EBV) genome is found in the majority (>90%) of B cell PTLD occurring early (within the first year) after solid organ transplantation. However, PTLD occurring later after transplant in adult populations is increasingly EBV- (4). PTLD encompasses a wide spectrum of clinical conditions characterized by lymphoproliferation after transplantation, which may or may not be symptomatic. These syndromes range from uncomplicated infectious mononucleosis to true malignancies (5-8). Disease may be nodal or extranodal, localized, often in the allograft, or widely disseminated. PTLD may resemble a self-limited infection or be indistinguishable from non-Hodgkin's lymphoma. Lesions may be localized and progress slowly or the patient may present with a fulminant multisystem sepsis-like syndrome.

EBV is known to play a major role in the development of EBV+ PTLD (9). The pathogenesis of these disorders is complex, and related to two unique characteristics of EBV, The first is the ability of the virus to transform and immortalize B lymphocytes, with resulting proliferation sometimes causing

secondary genetic or epigenetic mutations. The second relates to EBV's ability to protect against apoptosis in cells that would normally be destined for this fate. The pathogenesis of EBV-associated lymphomas involves a complex interplay between different patterns of viral gene expression and cellular genetic changes (9). However, in EBV-negative lymphomas, cellular genetic changes are wider and more complex than when the virus is present suggesting that in the multi-step process of malignancy development, genetic complementation directly by EBV in EBV+ PTLD can render some genetic changes present in EBV negative PTLD redundant (9-10).

A tolerogenic microenvironment appears to be important for PTLD pathogenesis (11-12). Immunomodulation caused directly by EBV viral proteins and the coordinated effects of viral and cellular miRNAs likely contribute to this effect (reviewed by Martinez; 13). In a study of immune checkpoint abnormalities in B-lymphoproliferative disorders across immunodeficiency settings, de Jong (6) found universal PD-L1 expression in tumor cells independent of both EBV status and morphologic classification. This expression appeared to result from copy number alterations in chromosome 9p24.1 containing the associated PD-L1/PD-L2 loci (6). De Jong suggested that this genetic abnormality might be a unifying pathogenesis for all immunodeficiency B lymphomas across a diffuse large B cell lymphoma (DLBCL) to classical Hodgkin lymphoma morphologic spectrum. There is also an increasing body of evidence that suggesting that chronic inflammation due to infectious and non-infectious causes might further contribute to lymphomagenesis (14). Innate and adaptive immune responses, particularly the EBV-specific CD8 T lymphocyte (CTL) responses are critical for controlling EBV infection; restoration of these responses is important for the treatment of EBV-related disorders (15).

Although B cell transformation and PTLD are a result of latent EBV infection, theoretical models of EBV biology suggest that lytic EBV infection may be important during primary EBV infection prior to the development of the CTL response (16). For a patient experiencing EBV infection for the first time in the early post- solid organ transplant period, delays in the development of the EBV-specific immune response may occur due to the exogenous T-cell targeted immunosuppression all patients receive; these responses may also be influenced by host genetic factors (17). Theoretically, this would prolong the one-way self-amplifying circuit of naive B cell infection, latency in memory cells and reactivation with infectious virus production. The resulting high virion peak results in massive infection of the B cell pool and perhaps other cells not normally infected by EBV (T cells, NK cells, memory B cells), thereby setting the stage for secondary events that lead to malignancy (14).

Although the role of EBV in the pathogenesis of EBV-negative PTLD is uncertain, gene expression analysis suggests that it is distinct from EBV+ PTLD and closely resembles EBV-negative lymphomas in the immunocompetent host suggesting a different pathogenesis (10). Chronic antigenic stimulation by the allograft including antibody mediated rejection has been hypothesized but not proven to play a role in the development of EBV-negative PTLD (4, 18).

We provide recommendations for the prevention, diagnosis and management of PTLD based on a literature review including guidelines published by other groups (e.g. the British Transplantation Society (19-20) and the ESCMID Study Group of Infection in Compromised Hosts (21).

Epidemiology and Risk Factors

Humans are the only known host of EBV. In the community, EBV is believed to be primarily transmitted by exposure to saliva. In developing countries, 90% of children are infected before age 5, typically acquiring infection in an asymptomatic manner. In developed countries this level of seropositivity is not attained until the fourth decade of life [reviewed by Odumade (22)]. In the transplant setting, donor-transmitted EBV infection is extremely common in EBV mismatched (donor seropositive/recipient seronegative) patients. Transmission is also possible when nonleukoreduced blood products are used.

The diagnosis of PTLD requires tissue examination. EBV can be detected in significant amounts in tissues such as the liver or gut yet not meet histologic criteria for PTLD diagnosis. This occurs most often in the setting of primary EBV infection and EBV DNAemia These diagnoses (EBV hepatitis or enteritis) are considered part of the spectrum of non-PTLD EBV disease after SOT. In some settings, tissue is not available or accessible. When laboratory evidence of EBV infection is present and other causes have been ruled out, the term EBV "disease" is also used to describe a number of clinical syndromes where EBV is believed to play a causative role.

Although the highest rate of PTLD in the solid organ transplant setting is seen in the first year after transplant, some analyses suggest that the incidence of this early PTLD (> 90% EBV-positive) is decreasing (4, 24-25). However, cases occurring in the first year after transplant represent only one-fifth of the total cumulative 10-year post transplant PTLD burden (26). Analyses of both French and ANZDATA

renal PTLD registries suggest a biphasic pattern of disease with a second peak occurring in years 7–10 after transplant after a period of reduced incidence in years 2–7 (23, 24). A significant proportion of late B cell PTLD is monomorphic and may be EBV-negative (~ 50%), with the relative proportion of EBV-negative lesions increasing over time after transplant as well as in the most recent era likely reflecting improved patient and graft survival (4, 27). NK or T cell PLTD (approximately 37% are EBV+) may also occur late after transplant (28).

PTLD incidence is also dependent on the type of organ transplanted, which may reflect immunosuppressive regimens, lymphoid load in the allograft and chronic antigenic stimulation resulting from direct communication and exposure to environmental antigens or chronic allograft dysfunction including antibody mediated rejection (4,26). Longer graft and patient survival may be exacerbating the latter effect. Small intestine transplant recipients are at the highest risk for development of PTLD (up to 32%), while recipients of pancreas, heart, lung and liver transplants are at moderate risk (3–12%). Renal transplant recipients are at relatively low risk (1–2%) (26). A recent single center report suggested after 10 years post-transplant, the cumulative incidence of PTLD in kidney transplant recipients may exceed that of liver transplant recipients (4). Caillard et al also described a temporal sequence of sites of PTLD involvement in adult renal allograft recipients, with disease localized to the graft occurring within the first two years, primary CNS lymphoma (PCNSL) occurring between years 2 and 7 and gastrointestinal disease occurring between years 6 and 10 and becoming the predominant site of late disease (24). This post-transplant timing of PCNS lymphoma was similar to that reported in a large retrospective case series, median time 54 months (29) but differs from that reported

in a study linking transplant and cancer registries in the United States where most cases of PCNSL occurred in the first 1.5 years (30). Although PTLD in solid organ transplant recipients is most often of recipient origin (31), PTLD limited to the graft occurring early after transplant is predominantly donor in origin (32).

Risk Factors: The risk factors for the development of early (<12 months after transplant) and late PTLD (>12 months after transplant) in solid organ transplant recipients are shown in Table 1 (4, 33-36).

Table 1

Risk Factors for PTLD in solid organ transplant recipients

Early PTLD
Primary EBV infection
Type of organ transplanted
(intestine> lung> heart> liver>pancreas> kidney)
Polyclonal antilymphocyte antibodies*
Young recipient age (i.e. infants and young children)
Late PTLD
Duration of immunosuppression
Type of organ transplanted
Older recipient age (i.e. adults)

Contradictory/controversial evidence exists for the role of the following as risk factors for PTLD: Tacrolimus in pediatric recipients; specific HLA epitopes ; HLA matching; certain cytokine gene polymorphisms; preexisting chronic immune stimulation; Hepatitis C infection; viral strain virulence (EBV1 vs. EBV-2 and viral gene mutations); CMV infection/disease.

*historical risk factor, no increased risk in most recent era when different formulations and lower doses are being used as induction therapy

Analyses of risk factors for PTLD have used both smaller single center and larger registry datasets. Both approaches have limitations and often involve specific subsets of patients, adults versus children or specific allograft types. Many of the

risk factors are interrelated and multivariate analysis is required to identify independent risk factors. Even using this approach, results are not always consistent (25, 37). An overwhelming risk factor in most analyses is EBV seronegativity pre-transplant and primary EBV infection, placing pediatric populations at higher risk of developing PTLD than their adult counterparts (4, 24-25,38). In a multivariate analysis of the Collaborative Transplant Study database an increased risk for non-Hodgkin lymphoma was observed in kidney and heart recipients if EBV seronegative pre-transplant (adjusted hazard ratio [HR] 6.5 and 3.6, respectively) but not in liver recipients (HR 0.6) (39). However, a subsequent multivariate analysis of the SRTR data in the United States confirmed an increased risk associated with being EBV-seronegative in kidney (HR 3.6), and heart (HR 4.0) but found a smaller but significantly increased risk in seronegative liver recipients (HR 1.5) (40). R+ are not devoid of PTLD risk and this risk appears higher in pediatric than adult recipients (39-41). This may in part be because seropositive infants < 12 months are misclassified because of passive maternal antibody (42) and because of significantly higher seroconversion rates in children compared to adults; some seropositive children may be recently infected when transplanted with incompletely developed immune responses (41). Using the OPTN/UNOS database to analyze PTLD rates in kidney transplant recipients seronegative before transplant, Sampaio et al observed among pediatric recipients that donor-seropositivity (D+R-) and donor-seronegativity (D-R-) resulted in comparable risks for PTLD at three years post-transplant, perhaps reflecting the high rate of community acquired infection in children. In contrast, in adults where the D-R- subset is likely to be very small, D-R- recipients trended toward having a lower risk of PTLD

than D+R- recipients which received statistical significance when a living donor was used (25). Intestinal transplant recipients, appear to have an exceptional high risk of PTLD development, independent of pre-transplant EBV serostatus. (43-45).

Although PTLD rates increased after calcineurin inhibitors became the backbone of most immunosuppressive regimens in the 1990s, it is likely that the net state of immunosuppression, an entity difficult to measure, is a major risk factor. Analyses that have attempted to quantify the risk associated with specific immunosuppressive agents used for induction or maintenance therapy have observed inconsistent results (reviewed by 37, 46-47). In the 1980s and early 1990s, potent monoclonal (OKT3) and polyclonal anti-lymphocyte globulins were used for induction therapy and treatment of rejection, often at high doses or in repetitive courses. These agents were associated with increased PTLD risk (33-34). However, from the late 1990's onward, rabbit ATG has become the predominant polyclonal agent used, at lower doses than those used historically. In the current era, analyses of PTLD risks associated with induction therapy, which more recently have included anti-IL receptor antagonists and alemtuzumab (48), have been inconclusive or contradictory (reviewed by 47). The largest study of induction therapy and PTLD risk was the Transplant Cancer Match Study which analyzed data from 111,857 kidney transplant recipients (1987-2009) (48). These investigators confirmed the historically observed increased risk of non-Hodgkin lymphoma with OKT3 (adjusted incidence rate ratio (aIRR of 1.37) and also found an increased risk with alemtuzumab (aIRR 1.79). However, they found no increased risk with polyclonal anti-T cell agents or IL2 receptor antagonists (48). .

Very high rates of PTLD presenting predominantly as primary CNS lymphoma were observed in renal transplant patients who received the co-stimulation blocker belatacept and were EBV seronegative prior to transplant, leading to warnings related to risk associated with the use of this agent in this subset of patients (49-51). The duration of immunosuppression and older recipient age are risk factors for late PTLD development. This highlights the need for studies to optimize minimization of long-term immunosuppression in individual patients including the accommodation of immunosenescence associated with aging in patients surviving for long periods after transplant. Cytomegalovirus infection may contribute to the net state of immunosuppression and has been described as a PTLD risk factor, but analyses of the impact of CMV disease or CMV mismatch from single center or registry analysis has been conflicting (46). Improvements in CMV prevention and managements may have impacted these analyses.

Manifestations of Non-PTLD EBV Syndromes

Although the most feared EBV-associated disease after transplantation is PTLD, patients may experience non-PTLD-related disease. The features of this might include the manifestations of infectious mononucleosis (fever, malaise, exudative pharyngitis, lymphadenopathy, hepatosplenomegaly and atypical lymphocytosis), organ specific diseases such as hepatitis, pneumonitis, gastrointestinal symptoms and hematological manifestations such as leucopenia, thrombocytopenia, hemolytic anemia and hemophagocytosis as well as more serious hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). Some of these manifestations may be identical to the features of PTLD (Table 2). EBV-associated post-transplant smooth muscle tumors can occur *de novo* or after

PTLD at a median interval of 48 months after transplant and develop earlier in children than adults. They can be of donor or recipient origin, and appear in atypical sites such as solid organs. When involving multiple sites, disease is multifocal rather than metastatic in origin (52).

Clinical Manifestations of PTLD

An adequate physical examination is required to detect the manifestations of PTLD, which may be quite nonspecific (Table 2).

Table 2

Presenting symptoms and signs in patients with lympho- proliferative disorder

Symptoms/complaints	Signs
Swollen lymph glands	Lymphadenopathy
Weight loss	Hepatosplenomegaly
Fever or night sweats	Subcutaneous nodules
Sore throat	Tonsillar enlargement
Malaise and lethargy	Tonsillar inflammation
Chronic sinus congestion and discomfort	
Abdominal pain	Signs of bowel perforation
Anorexia, nausea and vomiting	Mucocutaneous ulceration
Gastrointestinal bleeding	Mass lesions
Symptoms of bowel perforation	Focal neurologic signs

Given the predilection for the reticuloendothelial system to be involved, this clinical examination should include a meticulous assessment for lymphadenopathy and adenotonsillar hypertrophy. The general physical examination might elicit signs referable to the site(s) of organs affected by PTLD. An important component of the assessment is clinical staging as discussed below.

Diagnostic and Evaluative Tests

Blood tests (Non-EBV): Initial tests include a complete blood count with white blood cell differential. In the case of the latter, lymphopenia might suggest less overall CTL activity, which is essential in containing EBV-driven lymphoproliferation. In some patients with PTLD, there may be evidence of anemia, which is usually normochromic, normocytic, but may be hemolytic. In patients with gastrointestinal tract PTLD and occult bleeding over a prolonged period of time, there may be evidence of iron-deficiency anemia with hypochromia and microcytosis. The source of bleeding can be determined by performing additional testing, such as examination of the stools for occult blood. Thrombocytopenia has also been observed in non-PTLD EBV disease.

Depending on the location of PTLD lesions, there may be evidence of disturbances in serum electrolytes, liver and renal function tests. Elevations in serum uric acid and lactate dehydrogenase may occur. Serum immunoglobulin levels may be elevated as part of an acute phase reaction. The presence of concomitant CMV infection should be determined using plasma or whole blood quantitative nucleic acid testing for CMV DNA as well as the examination of biopsy tissue for evidence of CMV.

Other adjunctive tests that might predict PTLD risk have been investigated. Potential biomarkers studied include serum 1L-6 (53), serum/plasma free light chains (54), serum sCD30 (55), serum CXCL13 (56) and host genetic factors including HLA type (17) and polymorphisms in cytokine genes (57) but require

further validation. How these markers relate to each other and to EBV viral load in predicting PTLD risk should be the subject of future research.

Blood tests (EBV-related)

EBV serology: Determination of recipient and donor EBV serostatus using serology assays is important for risk stratification to inform prevention strategies. Anti-VCA IgG and anti-EBNA-1 IgG are serologic tests most often used for EBV serostatus assignment; some testing panels include anti–early antigen (EA) and anti-VCA IgM, more commonly used for diagnosing primary infection in immunocompetent hosts (22). Older, small studies suggested that some serology profiles might be useful for predicting PTLD but these have not been validated in larger cohorts. Carpentier et al observed that pediatric SOT recipients with high EBV viral load during primary infection who did not produce anti-EA were more likely to develop PTLD (prolife positive predictive value 75%) (58). In addition for seronegative patients failure to seroconvert and in seropositive patients, falling anti-EBNA levels when EBV viral loads were high have been observed in patients who developed PTLD (59).

EBV exposure history is difficult to determine in infants < 12 months because of the presence of maternal antibody. Pre- and post-transplant EBV serology results are also difficult to interpret in the presence of passive antibody from transfused blood and after receipt of immunoglobulin products. Direct measurement of EBV DNA in peripheral blood has replaced seroconversion for the diagnosis of primary EBV infection, as the latter responses are often delayed (60).

Detection of EBV nucleic acids or protein in tissue: Documenting the presence of EBV-specific nucleic acids in tissues is essential for the diagnosis of EBV-associated PTLD. RNA *in situ* hybridization targeting EBV-encoded small nuclear RNA (EBER; 61-62) is the preferred approach. EBV latent or lytic antigens can also be detected in fixed tissues by immunohistochemistry using commercial antibodies directed against EBNA-1, EBNA-2 and LMP-1 or BZLF1, respectively (61,63) and used to document the presence of EBV although these techniques are less sensitive than *in situ* hybridization. Direct EBV DNA amplification from tissue is less useful as it does not allow cellular localization or differentiation of EBV in lesions from that present in passenger lymphocytes.

***Viral load determination*:** The optimal way to perform, interpret and utilize quantitative EBV viral load assays for surveillance, diagnostic and disease monitoring purposes remains uncertain (64). In October 2011, the World Health Organization approved the 1st International Standard (IS) for EBV DNA for assay calibration. The goal of the IS was to reduce the historical extreme variability (usually in the range of 2-4 $\log_{10}$) in measurement results reported on individual samples when tested using the wide array of commercial and in house developed assays being used for quantifying EBV DNA in clinical specimens (65-66). Although preliminary evaluation of the WHO IS suggests that result harmonization among laboratories testing the same sample may have improved (67-68), significant variability does persist (69-71). Until the impact of the standard on result harmonization among a wider array of assays is validated using clinical samples, inter-institutional result comparison requires formal cross-referencing of measurement results between institutions. Data suggest that in most laboratories

intra-laboratory result reproducibility and result linearity over the dynamic range of the assay is reasonable (66, 70). Therefore trends in Individual patients over time determined using the same assay are valid and may be more useful than single values (72-73). Optimal extraction methods, gene targets and instrument platforms for EBV viral load assessments have not been determined. EBV viral load in whole blood and lymphocytes appears comparable and normalization of reporting units to cellular DNA does not change dynamic trending in individual patients (reporting IU/mL of whole blood is adequate) (74-75), controversy with respect to preferred sample type (whole blood vs. plasma) remains (76). Whole blood or lymphocyte EBV viral load is higher and becomes detectable earlier than contemporaneously tested plasma samples in longitudinally followed patients, making testing of this sample type more sensitive for early detection of primary infection and EBV reactivation events. Although, generally, EBV DNA becomes detectable in plasma as EBV viral load rises in matched whole blood samples, the quantitative correlation between EBV viral load measured in whole blood or lymphocytes versus plasma is suboptimal (74,77). However, plasma testing may have better specificity for the detection and monitoring of EBV-related disease including PTLD (76)

Studies of the sensitivity and specificity of quantitative EBV viral load for the diagnosis of early PTLD and symptomatic EBV infection are limited (77-- 80). Pediatric populations have been the focus of many of these studies. Based upon historical studies in high-risk asymptomatic solid organ transplant recipients being serially monitored, the use of EBV viral load as a diagnostic test (i.e. levels above a specific quantitative threshold being diagnostic of PTLD) has good sensitivity for

detecting EBV-positive early PTLD but misses EBV-negative as well as some cases of localized and donor-derived EBV+ PTLD. However, it had poor specificity, resulting in good negative (greater than 90%) but poor positive predictive value (as low as 28% and not greater than 65%) in these populations (81-82). When used in the diagnostic context, this would result in significant unnecessary investigation of patients for PTLD. However, with the overall reduction in early PTLD and introduction of pre-emptive therapies in many centers, the current sensitivity of high viral load as a predictor of PTLD may be lower (79-80).

Formal evaluation of EBV viral load assessments as a diagnostic tool using a single evaluation in patients presenting with symptoms and/or signs (usually mass lesions) with no history of recent or previous monitoring have not been carried out in populations at high risk for PTLD. In low-risk seropositive adult transplant recipients, high EBV viral load lacked sensitivity, understandably missing all cases of EBV-negative PTLD and some cases of localized EBV-positive PTLD, but was highly specific for EBV-positive PTLD (83). EBV viral load measured in plasma appears to improve the specificity of the test as a diagnostic tool for EBV-positive PTLD while not significantly lowering its sensitivity relative to assessments in cellular blood compartments (76-78, 83-84).

Data with respect to EBV viral load testing in samples other than peripheral blood, such as bronchoalveolar lavage (BAL) fluid or CSF are limited. Although in lung and heart lung transplant patients in whom the lung is often the primary site of PTLD, investigators suggested that high quantitative levels of EBV load in BAL fluid may be a more sensitive predictor of PTLD than peripheral viral load assays (85), EBV

load in BAL was not predictive of PTLD in a larger multicenter study of pediatric lung transplant recipients (86). Moreover, EBV DNA, often at high levels, was detected in BAL fluid of adult lung (87) and other transplant recipients in the absence of PTLD (88). In the HSCT setting Liu found that levels of EBV DNA were higher in CSF than blood and a better predictor of CNS disease. In addition declining viral load levels in CSF correlated with clinical response (89). However, further data regarding the sensitivity and specificity of testing in BAL and CSF are required in order to meaningfully interpret testing at these sites.

Adjunctive laboratory testing may improve the specificity of high viral load as a predictor of PTLD. The best studied and most promising are assays measuring T cell restoration or EBV-specific T cell responses (13 reviewed by Martinez 2017). Although data suggest that the specificity and positive predictive value of EBV viral load can be significantly improved by using concomitant EBV-specific T cell ELISPOT and tetramer assays, these assays may be more useful for disease occurring early after transplantation (90). These assays are non-standardized, complex, costly and difficult to implement in a routine diagnostic laboratory (19, 91). Simpler rapid assays to measure global and EBV-specific T cell immunity using commercial ATP release assays (Cylex Immuknow and T Cell Memory) have undergone preliminary evaluation as adjunct markers of PTLD risk when combined with viral load testing in pediatric thoracic transplant recipients but require further validation (92). Viral gene expression profiling in peripheral blood as an adjunctive test of PTLD risk has been studied (13 reviewed by Martinez 2017) and is still the subject of research. To date no distinctive pattern that is indicative of PTLD or PTLD risk has been demonstrated.

Radiographic imaging: Most centers employ strategies similar to those used for lymphoma staging in immunocompetent patients (93) for PTLD which include CT scans of the chest, abdomen and pelvis. Beyond this, the choice of tests depends largely on the location of suspected lesions and the historical sequence of prior radiographic testing. The utility of routine brain imaging in the absence of symptoms is uncertain but many experts recommend this as part of the initial work-up, as the presence of CNS lesions will significantly influence treatment and outcome; MRI may be preferred over CT scanning because of more precise lesion delineation with MRI (94). CT scanning of the neck may help to define the extent of oropharyngeal involvement or detect subtle early changes that necessitate biopsy to rule out PTLD.

Pulmonary lesions that are visible on chest radiographs may require high-resolution CT scanning for better delineation prior to biopsy. Furthermore, CT of the chest may reveal mediastinal adenopathy and small pulmonary nodules that are not visible on the plain chest radiograph. Suspected intra-abdominal lesions may be evaluated with ultrasonography and CT scanning. This is in addition to other modalities of assessment, including GI endoscopy in the case of intestinal hemorrhage, persistent diarrhea and unexplained weight loss, where necessary. Because of concerns regarding cumulative ionizing radiation exposure in children, MRI could be considered as an alternative to CT in evaluating non-pulmonary disease sites (94).

Positron emission tomography–computerized tomography (PET-CT) has emerged as a potentially useful test as an adjunct for diagnosis, staging and assessing PTLD treatment response (95-97). PET-CT has an estimated sensitivity and specificity for identifying PTLD of ~90 % (98-99) and may identify sites for possible biopsy (99). This imaging technology can also result in disease upstaging and identify occult PTLD (100-101). A recent report from a German registry of adult PTLD reported that end of treatment PET-CT had a 92% negative predictive value for disease relapse (102). However, additional validation of its utility is required in these settings across the known heterogeneous spectrum of PTLD lesions. A major disadvantage, of particular concern in children, is that the amount of radiation exposure is significantly greater than that associated with regular CT scans. Lymphoma guidelines in immunocompetent adult patients discourage routine post-treatment surveillance scans (93); data for PTLD are lacking. PET/MRI is being evaluated as an alternative to PET-CT in the setting of lymphoma.

Histopathology: Pathology is the gold standard for PTLD diagnosis (103). Although excisional biopsy is preferred, a core needle biopsy is acceptable when larger biopsies are impractical as in the case of allograft organ biopsy. The tissue specimen should be interpreted by a hematopathologist or pathologist familiar with histopathologic features of PTLD. Institutional protocols should be put in place to ensure that tissue is handled appropriately for ancillary diagnostic tests.

PTLD cases should be classified using the World Health Organization 2017 classification system for tumors of hematopoietic and lymphoid tissues (103). This system subdivides PTLD into four categories: non-destructive PTLDs (plasmacytic

hyperplasia, infectious mononucleosis, florid follicular hyperplasia), polymorphic PTLDs, monomorphic PTLDs (B cell, T cell and NK cell further classified according to the lymphoma they resemble in the immunocompetent host) and Classic Hodgkin lymphoma PTLD (Table 3). Reports from a 2015 workshop conducted by the Society for Heamopathology and the European Association of Heamopathology (SH/EAHP) provide further details regarding the WHO classification system including diagnostic uncertainties and the limitations of the histopathologic classification system across the PTLD spectrum (5-7). Currently the WHO system classifies immunodeficiency-associated lymphoproliferative disorders (IA-LPDs) separately for four immunodeficiency states (post-transplant, HIV, primary immune disorders and other iatrogenic). Diagnostic criteria and terminology differs in these settings despite shared histology, immunophenotype and genetics. Natkunam has recently proposed that further standardization of classification occur across immunodeficiency states by reporting the name of the lesion (using the PTLD framework), the associated virus and the specific immunodeficiency setting (104)

Table 3

Histopathological Classification of PTLD (2017 WHO classification system)*

Non-destructive PTLDs

- Plasmacytic hyperplasia
- Infectious mononucleosis
- Florid follicular hyperplasia

Polymorphic PTLD

Monomorphic PTLDs[a]

(classify according to lymphoma they resemble)

- B-cell neoplasms
  - Diffuse large B-cell lymphoma
  - Burkitt lymphoma
  - Plasma cell myeloma
  - Plasmacytoma
  - Other[b]
- T-cell neoplasms[a]
  - Peripheral T-cell lymphoma, NOS
  - Hepatosplenic T-cell lymphoma
  - Other

Classic Hodgkin lymphoma PTLD[a]

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[a] The ICD-O codes for these lesions ae the same as those for the respective lymphoid or plasmacytic neoplasm.

[b] Indolent small B-cell lymphomas arising in transplant recipients are not included among the PTLDs, with the exception of EBV-positive marginal zone lymphomas

*based on citation #103

Sharply circumscribed, painful EBV-positive (+) mucocutaneous ulcers involving the oropharyngeal mucosa, skin or gastrointestinal tract, have previously been described in patients with immunosenescence or receiving iatrogenic immunosuppression for autoimmune diseases and this diagnosis has been added to the 2017 WHO classification system in these setting (105). Because this entity has also been described in SOT recipients (5,106) and shares many features with polymorphic PTLD, Natkunam has suggested it be classified with polymorphic

PTLDs in his recent standardization initiative for IA-LPDs. EBV+ mucocutaneous ulcers occur in the absence of a tumor mass; patients have no involvement at other sites, no adenopathy and no detectable EBV DNAemia (106). Pathology is characterized by polymorphous infiltrate and atypical large B cell blasts co-expressing B-cell antigens and CD30, often with Hodgkin/Reed Sternberg (HRS) cell-like morphology (5). SOT patients with these ulcers responded to minimal therapeutic intervention including reduction in immunosuppression or rituximab monotherapy (106).

Because of the intrinsic limitations of a histopathologic classification system alone, additional pathologic tools, many of which are molecular, have provided a better understanding of the pathogenesis of specific types of PTLD (reviewed by 9-10). These tools include investigation of EBV clonality, strain typing and sequencing, and lytic and latency EBV gene expression. The PTLD tumor cell (donor versus recipient), and its origin relative to the germinal center have been studied. In addition, chromosomal mutations and profiling of the expression of cellular genes and oncogenes related to signaling pathways and lymphomagenesis have been examined. Recently, studies of immune evasion/exhaustion markers on tumor cells as well as infiltrating (non-tumor cells) in lesions have been performed. It is hoped that some of these tools, which require further validation, might improve tailoring of treatment and improve patient outcomes (reviewed in 9, 10).

Recurrent PTLD may represent true recurrences (morphologically and clonally identical to the original tumor), PTLD in a more aggressive form or the emergence of a second primary tumor such as an EBV-associated post-transplant smooth

muscle tumor (EBV-SMT). For this reason, biopsy of such recurrences is encouraged.

Recommendations – Diagnostic and Evaluative Testing

1. We recommend that EBV serostatus should be determined on all transplant recipients and donors in order to identify the patients at high risk for PTLD development (Strong/high). Seropositive recipients < 12 months of age should be considered seronegative and seropositive donors < 12 months should be considered EBV seropositive for purposes of risk stratification (**strong/low**). Patients seronegative prior to transplantation should be rescreened while on the waitlist and yearly after transplant to determine ongoing susceptibility to primary infection (**weak/low**).

2. We recommend that in settings where quantitative EBV viral load testing is recommended, it should be performed using assays calibrated to the WHO IS for EBV DNA (**strong/moderate**).

3. Because validation of the impact of the WHO EBV DNA IS calibration on result harmonization among assays is limited, we recommend that patients should be monitored using the same sample type and the same assay in a single laboratory **(strong/moderate)**. If inter-laboratory result comparison is required, formal cross-referencing of results among the laboratories using clinical samples should be performed. (**strong/low**)

4. We recommend histopathologic examination of tissue (preferably an excisional biopsy) as the gold standard for PTLD diagnosis and recommend PTLD classification using the latest WHO system (103) **(strong/ moderate)**. Further standardization of this classification system as suggested by Natkunam (5) should

be considered. Routine studies should include hematopoietic lineage determination, EBV genome and anti-CD20 detection **(strong/ moderate)**. EBV viral load testing is not recommended as a routine adjunctive diagnostic test for PTLD **(weak/low);** negative EBV DNAemia measured in whole blood is a good negative predictor of EBV+ PTLD early after transplant in seronegative children at high risk.

5. When possible re-biopsy of recurrent PTLD should be undertaken to rule out evolving PTLD pathology and a second primary tumor, such as EBV-SMT (strong/ moderate).

Clinical staging of PTLD

Once the pathologic diagnosis of PTLD is confirmed, staging that documents the presence or absence of symptoms, the precise location of presumed or proven PTLD lesions, the involvement of the allograft and the presence of CNS involvement is undertaken prior to treatment in most centers. Stage IV disease with CNS or bone marrow involvement was found to be an independent predictor of survival in an analysis of data from a German pediatric PTLD registry (107). However, no staging system for PTLD has been validated that alters treatment approach or is prognostic with respect to survival. Most centers use systems that have been developed for lymphoma staging in immunocompetent hosts, the Lugano classification system in adults (93) and the International pediatric non-Hodgkin lymphoma staging system (IPNHLSS) in children (108). The need for routine bone marrow biopsy and lumbar puncture for staging particularly in the absence of symptoms or signs of involvement at these sites is uncertain; routine bone marrow biopsies are not recommended in immunocompetent hosts with DLBCL if PET-CT is performed (93)

Recommendations

1. We recommend staging of PTLD prior to initiation of treatment that includes CT imaging of chest, abdomen and pelvis (**strong/low**). MRI of the brain may be also be useful for staging (**weak/very low**). PET-CT may provide additional useful information for staging and end of treatment response assessment in adults (**weak/moderate**) and children **(weak/very low)**.

Prevention of PTLD

Although some centers employ chemoprophylaxis and/or preemptive strategies using EBV viral load as a surveillance tool, for the prevention of this complication, published data in the form of prospective controlled trials in support of these protocols are currently limited and the role of antiviral agents is controversial. Potential strategies for prevention are listed below.

General

Identification of patients who are also at risk of primary EBV infection would select a particularly vulnerable subgroup of recipients since being seronegative has been identified as the greatest risk factor of EBV-positive PTLD. Such patients should be monitored carefully for clinical symptoms/signs (fever, diarrhea, lymphadenopathy, allograft dysfunction, etc.) and investigated aggressively for PTLD when these develop. Because PTLD frequently presents with allograft dysfunction and acute rejection is in the differential diagnosis, it is important to make a pathologic diagnosis of rejection using standardized criteria including studies that that detect EBV in tissues to clearly distinguish early PTLD from rejection prior to the use of more potent antirejection therapy.

Antiviral prophylaxis

Chemoprophylaxis: The antiviral drugs acyclovir and ganciclovir inhibit EBV lytic replication but have no effect on latent infection (22). Despite the fact that many centers use universal antiviral prophylaxis for high-risk EBV mismatched transplant recipients, this strategy remains controversial and has not been adequately evaluated in randomized controlled trials. Although a number of single or multi-center retrospective SOT studies suggested antivirals reduced the incidence of PTLD (reviewed by 1, 109), this was not observed in an analysis of kidney transplant registry data (110). A prospective randomized controlled trial in 48 liver transplant recipients comparing two weeks of intravenous ganciclovir alone to two weeks of ganciclovir followed by 50 weeks of oral acyclovir demonstrated no difference in the incidence of EBV disease in either group but lymphoma was not diagnosed in either arm of the study (111). A recent meta-analysis suggested that antiviral use, both prophylactically and pre-emptively in patients EBV seronegative prior to transplant did not impact the incidence of PTLD (109).

Since primary, often donor-transmitted, EBV is a major PTLD risk factor, reducing donor-derived EBV transmission may extrapolate to reduced PTLD risk. A reduction in primary EBV infection was observed in an analysis of ganciclovir/valganciclovir prophylaxis versus no prophylaxis in 28 mismatched pediatric kidney SOT recipients, although receipt of antivirals was not randomized (60). However, this effect was not observed in a similar study in 73 adult kidney or kidney-pancreas recipients (112). Historically the median time of onset of primary EBV infection after solid organ transplantation was 6 weeks and reactivation/infection events were most often observed in the 2–3-month period after transplantation. Recent studies in patients

monitored serially using EBV viral load, note later initial detection of EBV DNAemia at a median of 110 days (113) and a mean of 276 days (114). This delay has been attributed to receipt of antiviral prophylaxis in an adult cohort of kidney transplant recipients (112) but was not observed in a similar pediatric cohort (115). The timing of EBV reactivation in the donor organ is unknown and may occur very early, even in the allograft before transplant. Two pilot studies in the setting of adult kidney recipients of living donors provide intriguing but very preliminary results suggesting that treatment of the donor or recipient pre-transplant might impact PTLD or EBV transmission. The first involved randomized treatment of the donor with two weeks of valganciclovir (116), the other treated the recipient with a single dose of rituximab four weeks before transplant (117). These preliminary observations require further evaluation, ideally in multicenter randomized controlled trials.

Immunoprophylaxis: The prophylactic benefit of IVIG on PTLD also remains uncertain. Two prospective randomized placebo-controlled trials in EBV seronegative patients evaluating CMV-IVIG alone (118) or IVIG in recipients already receiving antivirals (119) failed to observe an effect on either EBV disease, PTLD rates or EBV viral load kinetics. In contrast, registry data analysis found a significant reduction in PTLD incidence in kidney transplant recipients receiving IVIG although this protective effect did not extend beyond the first post-transplant year (111).

Preventing EBV primary infection and/or boosting EBV immunity to prevent EBV disease using active immunization with an EBV vaccine would be particularly useful in SOT (120-121). To date, EBV vaccine efforts have focused on EBV gp350, which contains major neutralizing epitopes. A phase II clinical trial with a candidate

vaccine reduced the incidence of infectious mononucleosis but not EBV infection. A small phase 1 trial in which the EBV gp350 vaccine was administered to EBV seronegative children with renal failure awaiting transplant found suboptimal immune responses that waned very quickly; however vaccine dose and adjuvant were likely not optimal (122). Research with modified formulations of the gp350 vaccine and alternate vaccine candidates are ongoing (121)

Preemptive management: Pre-emptive PTLD prevention strategies combine serial quantitative EBV DNA monitoring in peripheral blood with interventions that might lower risk, triggered by EBV DNA levels predictive of PTLD development occurring before onset of clinical disease. Evidence for use of this approach is greatest in high risk patients, which in the SOT setting includes EBV seronegative recipients, particularly those receiving seropositive donor organs (4, 24-25,40,123-125) and possibly all intestinal transplant recipients (43). Although mean and median peak EBV viral loads are higher in mismatched patients as are high persistent high viral loads (> 5 $\log_{10}$ copies/ ml of whole blood) in patients who were EBV-seronegative pre-transplant than in patients who were seropositive pre-transplant, high viral loads in the range of 4-5 $\log_{10}$ or greater can be observed in the latter group (126-130) Although PTLD does occur in patients who were EBV-seropositive pre-transplant, their risk is significantly lower than their EBV-seronegative counterparts (4). Moreover, elevated and often sustained elevation in EBV loads have been observed in 67%-72% of adult liver (127-128), 31%-29% of adult kidney (129-130) and 13%-42% (assay dependent) (83) of adult lung transplant recipients EBV-seropositive pre-transplant and appears to be a poor marker of future PTLD risk.

In addition to issues related to EBV assay standardization and specimen type outlined in the diagnostic section above, optimal pre-emptive monitoring algorithms have not been defined. Monitoring is most cost-effective when used during the highest post-transplant period for EBV+PTLD risk, which is the first year post-transplant in SOT. However, specific intervals during this period in which EBV DNA is first detected in blood in EBV-mismatched patients on and off antiviral prophylaxis require clearer definition in order to appropriately determine period when most intensive surveillance might be required. Similarly, better information on timing and risks of community-acquired EBV infection in seronegative children receiving seronegative donor organs might better inform development of an appropriate monitoring algorithm in this cohort. Viral load can rise very quickly with short intervals between detection of EBV DNAemia and EBV disease but this most often occurs in the HSCT rather than SOT setting. Viral load kinetics may be as important as absolute quantitative values for triggering interventions. In a Korean study analyzing results reported on samples submitted from both SOT (predominantly pediatric liver transplant) and HSCT recipients, neither specific initial loads, peak load, nor rate of rise viral load could be defined that were clinically useful with respect to sensitivity or specificity for PTLD prediction using ROC analysis in the SOT cohort (131). However, the pre-transplant serology of the SOT patients being monitored and evaluation of sample submission bias in that study were not available. Although frequent (weekly) monitoring over the high-risk period has been suggested by some investigators, there are no data to suggest that less frequent monitoring (i.e. biweekly or at even longer intervals later in the first year after transplant) negatively impacts preemptive management.

There are very few natural history studies relating EBV DNAemia levels to PTLD events where clinicians were blinded to results. Result interpretation from studies not blinded is complicated by the heterogeneity of the populations studied, non-standardized assays and sample types used (81). As a result of these factors, optimal trigger points for pre-emptive interventions cannot be clearly defined (3, 132). It can be argued that any detectable peripheral EBV viral load in the setting of a primary EBV infection should trigger review and transient minimization of immunosuppression when possible, taking into account the significant immunodulatory effects of EBV itself, in order to optimize opportunities for development of EBV-specific adaptive immune responses.

There are neither randomized controlled trials comparing pre-emptive prevention strategies to placebo nor specific interventions to each other. Reduction in immunosuppression (RIS) is the initial intervention most often used for pre-emptive therapy in SOT (133). This is based on a reduction in early PTLD incidence in high risk populations compared to historical control populations (134-136) or contemporaneous patients who did not receive the intervention (43). Antiviral drugs (ganciclovir/valganciclovir) or intravenous immunoglobulin (IVIG) are sometimes also given in these studies (43, 135), often simultaneously with RIS. The added benefit of these agents is uncertain (134, 136); antiviral drug dosing is also uncertain. The use of historical controls in assessing efficacy of pre-emptive interventions is problematic, as the incidence of early PTLD appears to have also decreased in adult SOT patient cohorts who were not being monitored (4); this epidemiologic trend has not been specifically studied in non-monitored pediatric patients .

The process for optimal RIS in SOT recipients is uncertain (19, 137). In transplant recipients, conversion to mTOR inhibitors has been proposed due to the anti-proliferative and antiviral effects of these drugs although they have not been clearly shown to reduce and may actually increase PTLD risk (138-140). Because of this, pre-emptive strategies in some SOT centers include a change in immunosuppression to mTOR inhibitors often as monotherapy, which also likely represents an overall RIS (133)

HSCT recipients at high risk of PTLD also have high GVHD risk and often fail RIS because their immune systems are not reconstituted during the highest risk period. Therefore, the use of rituximab has evolved to become a common initial pre-emptive intervention in the HSCT setting (141-142); optimal dosing, however, remains uncertain (143). Rituximab is used less frequently in SOT recipients (133). Single center experiences have reported reduction in PTLD rates with rituximab use in heart transplant recipients failing RIS compared with historical controls (136) and EBV-mismatched kidney transplant patients given rituximab simultaneously with RIS compared with contemporaneous patients who were not treated (144). Safety concerns associated pre-emptive rituximab have arisen including possible excess bacterial infection due to delayed immune reconstitution, (145) and CD20 escape mutants causing PTLD (146). Hypogammaglobulinemia and progressive multifocal leukoencephalopathy have been described in other populations receiving this drug.
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Adoptive immunotherapy using either in vitro expanded autologous or HLA-matched banked third party donor polyclonal EBV-specific CTLs has also been used for PTLD prevention, given either to all high risk patients, or pre-emptively in

response to EBV DNAemia (see treatment section) (147). This prevention approach has been most extensively evaluated in HSCT recipients and is currently most commonly used when rituximab pre-emption fails; data in SOT recipients are limited. Only one case of PTLD has been observed in 108 HSCT and 21 SOT high risk patients who received EBV –CTLs prophylactically; that patient had received a CTL line that lacked strong EBV specificity (147). Access, cost and lack of definitive evidence of effectiveness in the SOT population prohibit widespread implementation of this approach.

Pre-emptive strategies have historically been targeted at preventing early PTLD. A significant number of transplant recipients, particularly those who experience primary EBV infection or EBV-positive PTLD have sustained elevation of EBV viral load after asymptomatic infection or resolution of EBV disease /PTLD with "set point" viral loads associated with persistent EBV infection significantly higher than those seen in EBV seropositive immunocompetent patients. Viral loads can persist, sometimes at very high levels, for many years in some patients. These SOT recipients are said to have a chronic viral load phenotype (CVLP); the pathogenesis of this state is unknown. The detectable viral load appears to be predominantly in memory B cells with type 0 latency gene expression (148-150). A study in thoracic pediatric chronic high load carriers suggest that many although not all have high frequencies of activated but functionally exhausted EBV-specific cytotoxic T cells based on expression of PD-1 and low levels of CD127 (149). However, Moran et al demonstrated that PD-1 expression on CD8+ T cells increased after transplant in renal transplant patients regardless of whether patients had CVLP or not (150).

Although studies in recipients of pediatric heart transplantation suggest that patients who are chronic high viral load carriers) may be at significantly increased risk of late onset EBV-positive PTLD (79,151), this risk appears in part to be organ-specific with intermediate risks observed in intestinal transplants (152) and low to negligible risk in pediatric liver (147, 153) and kidney (80,115,154,155) transplant recipients . However, even among specific allograft types such as pediatric liver transplant recipients, reported risks differ among centers (153,156). Although RIS may lower viral loads early after primary infection, even total withdrawal of immunosuppression does not appear to impact high viral "set points" at least in the short-term (157) and may precipitate rejection events (79). Additional data from prospective studies are required to determine the pathogenesis and natural history of CVLP in relationship to future PTLD risk in specific allograft types. This might determine whether ongoing viral load monitoring is useful and whether pre-emptive interventions can alter EBV load and future PTLD risk in CVLP patients.

Recommendations: prevention

1) The use of antiviral agents, IVIG and adoptive immunotherapy as universal prophylaxis for early PTLD prevention in EBV mismatched patients is not recommended (**weak/low)**

2) We recommend EBV viral load surveillance and pre-emptive interventions in patients who are EBV-seronegative pre-transplant (**weak/low**). In patients who receive seropositive donor organs, monitoring should occur weekly to biweekly, when possible over the first post-transplant year until EBV DNAemia is detected. When this occurs monitoring should occur weekly during initial acute phase of infection, then less frequently by increasing increments until "set point" is achieved

(**weak/very low**). Less frequent initial monitoring (monthly) for community-acquired infection should be considered in seronegative patients who receive seronegative donor organs. Ongoing monitoring beyond the first post-transplant year may be considered in patients who have fluctuating immunosuppression, rejection episodes or have not established a viral" set point". There are insufficient data to make recommendations regarding the preferred sample type (plasma or whole blood) to be used for viral surveillance and specific quantitative viral load levels that should trigger interventions.

3) Viral load surveillance and pre-emptive strategies are not routinely recommended for SOT patients who are EBV seropositive pre-transplant (adults: **strong/low**, children: **weak/low)** with the exception of intestinal transplant recipients (**weak/ low**) and in situations where retransplantation occurs following PTLD (**weak/low**).

4) We recommend RIS as the preferred pre-emptive intervention (**weak/low**). There are not sufficient data to either prescribe specific protocols for immunosuppression reduction or provide recommendations for or against switching to an mTor inhibitor. There are also not sufficient data to allow us to make recommendations for or against the use of rituximab in patients not responding to RIS or for the adjunct use of antivirals. Antiviral therapy as a sole pre-emptive intervention is not recommended (**strong/ very low**)

5) While ongoing EBV viral load surveillance for patients with persistently elevated set-point viral load late after transplant when acute primary or reactivation infection have resolved is an important research priority to understand the natural history and

biology of this state, the risk versus benefit of pre-emptive interventions such as lowering immunosuppression in this setting is uncertain; thus, ongoing viral surveillance with pre-emptive interventions is not routinely recommended (**weak/ very low**).

Treatment of PTLD

PTLD treatment remains a challenge. Although randomized controlled studies directly comparing treatment approaches are lacking, over the past decade there have been a number of larger prospective multicenter phase II trials that have provided valuable information to better inform management. These data have recently been reviewed for both adult (158-160) and pediatric transplant recipients (161-162) Despite this, optimal therapy for all the variable forms of PTLD that results in sustained remission, preserves allograft function and minimizes treatment toxicity remains elusive. Due to the complexity of PTLD treatment, the initial evaluation and management of such patients should be done by or under the supervision of a tertiary transplant center and involve a multidisciplinary team that includes transplant physicians, oncologists and infectious disease specialists.

The general approach to therapy involves a step-wise strategy starting with reduced immunosuppression, with escalation of treatment based largely on the clinical response and the histopathologic characteristics of the PTLD. Opportunistic infections, particularly *Pneumocystis jirovecii* pneumonia and *C. difficle* are common adverse events during PTLD treatment when cytotoxic chemotherapy is used (163-164). The need for additional prevention/prophylaxis strategies should be reviewed in all patients.

Reduction of immunosuppression (RIS): Over the past 30 years, RIS has been a common initial approach to PTLD management, but reported response rates have been highly variable (0–73%), likely reflecting the heterogeneity and size of the populations studied and the non-standardization of immunosuppression reduction. Among the largest studies examining this issue is a recent single center report that retrospectively analyzed outcomes in 67 adult solid organ transplant PTLD patients managed with a standardized approach to immunosuppression reduction alone as initial therapy (165). An overall response rate of 45% (37% complete response) was observed; patients who achieved complete remission had relapse rates of 17%. Although neither EBV detection in tissue nor B cell histologic subtype influenced outcome, bulky disease, advanced stage and older age predicted lack of response. Of concern were the high rates of acute rejection (32%) observed. It is unclear whether these data are applicable to pediatric populations who are more likely to experience PTLD in the context of primary infection.

The optimal strategy for immunosuppression reduction is uncertain and may be allograft specific, depending on the comfort of the physicians in risking acute rejection events. Suggestions for reducing immunosuppression based on expert opinion are outlined in the British Transplantation Society PTLD management guidelines (19). In a recent multicenter treatment trial (164), common approaches used included reduction of calcineurin inhibitors by 30-50% and discontinuation of anti-proliferative agents (azathioprine and mycophenolate mofetil). Switching calcineurin inhibitors to mTOR inhibitors is a strategy that has sometimes been used either when disease is still active or for ongoing maintenance therapy; evidence for a beneficial impact of this approach is lacking. The time period one should wait

before proceeding to alternative therapeutic interventions is also uncertain. Most patients would be expected to show evidence of a clinical response to reduced immunosuppression within 2–4 weeks (165). In a recent clinical trial, RIS failure was defined as stable disease at 2-4 weeks or progressive disease at any time (164). However, in the study by Reshef et al. (165), the median time to failure in non-responders was 45 days; therefore, waiting up to 6 weeks in stable patients without evidence of progressive disease could be considered.

Surgical resection/ irradiation (local and systemic): Complete or partial surgical resection, as well as local radiotherapy, have been used as adjunctive therapy along with reduced immunosuppression (166). When surgical excision or radiotherapy has been used for localized disease, long-term remission in the absence of additional therapy has been observed (167,168). However, RIS also often occurs in this setting, making it difficult to attribute remission to surgery and radiotherapy alone. Surgery is an essential component of the management of local complications such as gastrointestinal hemorrhage or perforation. Rossingol reported a small series of 8 adult patients with a 62.5% response rate after receiving radioimmunotherapy (^{90}Y-Ibritumomab Tiuxetan) with rituximab refractory/relapsed CD20-positive PTLD, presenting an additional potential option for patients unable to tolerate cytotoxic chemotherapy (169). However cost and accessibility of this therapy may make it difficult to implement outside of a clinical trial format.

Antiviral agents, Immune Globulin and Monoclonal Antibodies: Acyclovir and ganciclovir have been used in the management of early PTLD, alone or in combination with immune globulin (1,170). Currently, when antiviral agents are

employed, the agent of choice is ganciclovir, as *in vitro* it is 10 times more active against EBV compared with acyclovir. Although latent viral infection predominates in PTLD lesions, lytic virus gene and protein expression is also seen in a significant proportion of cases (171-173) particularly those with an IgM+ phenotype (173). The contribution of antivirals to the treatment response is uncertain; there is no evidence to support the use of antiviral agents in the absence of other interventions such as decreasing immunosuppression or anti-CD20 therapy. Arginine butyrate, a histone deacetylase inhibitor induces the lytic cycle of EBV, making EBV-infected cells sensitive to ganciclovir. A phase I/II trial of arginine butyrate combined with ganciclovir demonstrated overall response rates in 10 of 15 patients with EBV+ lymphoid malignancies; one third had PTLD (174). This agent is no longer available for use in clinical settings. Another chemotherapeutic agent, the proteosome inhibitor bortezomib, also induces lytic virus replication in EBV infected cells and is being evaluated in clinic trials of gamma-herpesvirus associated malignancies including PTLD (175).

Monoclonal B cell antibody therapy (Anti-CD20): Although single agent rituximab, an anti-CD20 humanized chimeric monoclonal antibody, is rarely effective in the treatment of high grade B cell lymphomas in the immunocompetent patient, complete and sustained responses have been observed using this treatment approach in PTLD, after RIS. Three prospective phase II rituximab monotherapy trials demonstrated a combined overall response rate of 55% (reviewed by 2). Although treatment is well tolerated, relapse is frequent after four weekly doses of rituximab, with 25% of patients who had partial or complete responses showing evidence of disease progression by one year after treatment in one study (176). In a large

retrospective review early rituximab therapy improved progression free and overall survival (177). Gonzalez-Barca (178) reported complete response rates improving from 34.2% to 60.5% with a further four doses of rituximab in patients who achieved partial remission with the initial four doses. There is limited evidence to suggest that relapsed patients can sometimes be successfully retreated with single agent rituximab (179). In a phase II prospective multicenter CD20+ PTLD (both tissue EBV+ and EBV- included) treatment trial of 4 weeks of rituximab therapy followed by four sequential cycles of rituximab/CHOP every 3 weeks (cyclophosphamide, doxorubicin, oncovin and prednisone [CHOP-21]) called sequential therapy, the first 4 weeks of rituximab correlated with survival (163). This led to a second phase II trial using an approach known as risk-stratified sequential therapy (RSST), whereby patients who achieved complete remission with an initial four weekly doses of rituximab received four additional doses of rituximab at three weekly intervals without chemotherapy. Patients with evidence of disease progression on re-staging went on to receive four cycles of rituximab plus CHOP -21 [R-CHOP-21]. The results of this trial demonstrated that 25% of patients do not need chemotherapy and suggested that rituximab consolidation (eight not four courses of rituximab) led to improved time to progression by preventing relapse (164). Response to rituximab regardless of tissue EBV status of the PTLD continued to be a predictor for overall survival.

Data on rituximab monotherapy in pediatric PTLD populations are more limited in the form of case reports and retrospective case series. Larger studies include a study of 40 SOT PTLD patients in the US (180); 69% of children achieved complete remission, 16% partial remission. In a smaller study of 17 patients with lymphoproliferative

disorders in the UK (181), (includes HSCT, SOT and immunodeficiency patients) complete and partial responses were seen in 46.7%. Although the need for consolidation rituximab therapy is unknown, in the German Ped-PTLD (after SOT) 2005 study (182), 64% of patients achieved complete or partial remission after 3 doses of rituximab and 84% remained in remission after an additional 3 doses.

There is a growing body of evidence in support of the use of rituximab as the next step in the treatment of most CD20+ B cell PTLD when RIS does not result in complete remission. Potential adverse events associated with rituximab include a tumor-lysis like syndrome, prolonged depletion of B cells with protracted hypogammaglobulinemia, intestinal perforation, CMV reactivation, and progressive multifocal leukoencephalopathy. Although experience with the use of this agent is increasing, there is an ongoing need for additional data from prospective clinical trials, particularly in pediatrics.

Cytotoxic chemotherapy: Historically small retrospective studies reported complete remission rates varying from 42–92% for adult patients receiving cytotoxic combination chemotherapy, usually CHOP but also ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone) and ProMACE CytoBOM (mechlorethamine, doxorubicin, cyclophosphamide, etoposide, vincristine, prednisone, procarbazine, methotrexate, cytarabine, bleomycin) (reviewed by 183). The EBV-association of the PTLD did not impact response, when studied. Although this approach resulted in better long-term disease control than rituximab monotherapy, treatment related mortality was high at 13–50%, usually from infectious complications. Recently in a larger prospective phase II trial , in which 74 adult

patients with ECOG >2 received sequential treatment with both rituximab followed by CHOP-21 as described above with an overall response rate of 90%, complete response rate of 68%, and a median overall survival of 6.6 years was observed (163). This was better than the response of rituximab monotherapy followed by chemotherapy at relapse. However, CHOP treatment-related mortality was 11% and serious infections were observed in 41% of patients suggesting that a more tailored approach that identifies patients who may have sustained responses to rituximab monotherapy alone and avoid the toxicity of chemotherapy might be preferred. A follow-up phase II prospective study (RSST) included 152 adult PTLD patients receiving R-CHOP21 chemotherapy only if they had disease progression after rituximab monotherapy. In this trial patients had a similar overall response rate (88%), complete response rate (70%) and overall survival (6.6 years). Moreover, the serious infection (34%) and treatment-related mortality 8% were lower in the RSST trial (164).

In pediatric PTLD populations, less intensive chemotherapy regimens than those employed to treat lymphoma in immunocompetent children have been used. Multicenter prospective studies using six cycles of low dose cyclophosphamide and prednisone with and without rituximab after failure of initial therapy, most often RIS, have been reported (184-185). Response rates (67%, 69%) and relapse rates (19%, 8%) without and with rituximab, respectively, were observed. Addition of rituximab therapy appeared to add efficacy to the management of fulminant disease which was not responsive to low dose chemotherapy alone. Use of conventional dose chemotherapy in pediatric PTLD is generally reserved for those failing low-dose cyclophosphamide therapy.

Cytotoxic chemotherapy using the regimens outlined in the studies of adult and pediatric studies described above should be considered in patients with CD20+ B cell PTLD disease progression despite RIS and rituximab therapy. Conventional chemotherapy recommended for immunocompetent patients is most often used in CD20- B cell (including plasmablastic, plasma cell myeloma/ plasmacytoma-like PTLD), T cell PTLD, Hodgkin and Burkitt lymphoma. However, small case series have suggested that localized extra-nodal plasmacytomas could be successfully treated with RIS, surgery and/or irradiation (186). Similarly, small case series have reported successful treatment of Burkitt lymphoma using less intense chemotherapy regimens (reviewed by Dierickx, 159).

Other treatment modalities

Adoptive immunotherapy: Adoptive immunotherapy using donor derived cloned EBV-specific cytotoxic T cells (CTL) has been used successfully for the treatment of PTLD in allogeneic HSCT recipients, but in the SOT setting experience is more limited (147). Obstacles include the fact that PTLD lesions are usually of recipient origin in contrast to donor origin in the HSCT recipient and cell lines cannot be generated after rituximab therapy and T cell depleting regimens Although modifications to culture conditions, peptide pools or the use of genetically modified dendritic cells may increase the success rate of generating cell lines ex vivo from naïve T cells, in the SOT setting cost and time required to clone cell lines may also limit the utility of this approach (147), Use of banked third-party, allogeneic EBV-specific CTL selected by best available HLA match is an alternate approach. In a phase II clinical trial involving 33 patients (2 HSCT, 31 SOT) who had failed conventional therapy with immunosuppression reduction, rituximab, chemotherapy,

and/or radiotherapy using such CTLs, a 52% response rate at 6 months, with 14 patients achieving a CR was observed including; responses in CNS PTLD were also seen. Responses were superior with better HLA-matching between the recipient and the CTL donor (187). An even better overall remission rate of 80% with 86% five year survival was reported in a retrospective study of 10 children with PTLD who had failed RIS and rituximab therapy given third party donor EBV-CTLs (188) confirming the results of previous smaller studies (189,190), although a delayed response to earlier therapies cannot be ruled out in this cohort.

Notable developments that might improve the in vivo efficacy of adoptive therapy include genetic manipulation to create CTLs resistant to immunosuppressive drugs such as CNI and mTor inhibitors as well as MMF (191) and the availability of banked third-party virus-specific T cells with simultaneous activity against other viruses (CMV and adenovirus) that can also cause serious disease in both SOT and HSCT recipients (192).

Immunomodulatory/Anticytokine therapy: Historically, positive responses have been reported in small numbers of PTLD patients using ***a***lpha interferon (193) and anti-IL-6 (194) therapy but these agents are no longer commonly employed in the treatment of PTLD. A tolerogenic microenvironment is believed to be important for PTLD pathogenesis. High rates of PD-1 expression in infiltrating cells and/or PDL-L1/L2 on tumor cells in PTLD cases have been reported (6, 195). This suggests the potential for disease response to PD-(L)1 blockade using immune checkpoint inhibitors (pembrolizumab, nivolumab) in settings of refractory disease positive for these markers. However, in the transplant setting safety concerns are significant in

the form of precipitating rejection or exacerbating autoimmune disease that is often the cause of end organ failure requiring transplant. This therapy should be considered only in the context of clinical trials.

Treatment of CNS disease: CNS PTLD is a rare disease presenting as isolated primary CNS lymphoma (PCNSL) or with extra-cranial involvement. Clinical trial data and standardized management approaches that might inform optimal treatment approaches are lacking. In the largest multicenter retrospective study of 84 cases of PCNSL in SOT recipients treated with a variety of regimens, the overall response rate was 60% with a 43% three year overall survival. Response to first line therapy was the strongest predictor of survival (29). Current recommendations for treatment of CNS PTLD are extrapolated from the experience with PCNSL in immunocompetent patients where phase II trials identified induction therapy using the MATRix regimen (high dose methotrexate and cytarabine combined with rituximab and thiotepa) (196) followed by consolidation therapy that includes either whole brain radiotherapy (WBRT) or myeloablative chemotherapy with autologous stem cell transplant (197) as the preferred treatment. However, WBRT is associated with significant neurotoxicity particularly in older patients and the renal and hepatotoxicity associated with induction chemotherapy can be difficult to manage in a transplant setting. RIS in an initial therapy used in most patients (29). The inability of rituximab to cross the blood–brain barrier has raised concerns that levels achieved with systemic use alone are unlikely to have clinical efficacy in CNS PTLD. Despite this, Cavaliere (198) observed surprisingly good outcomes in seven of eight SOT recipients with PCNSL treated with primary rituximab monotherapy, often with RIS in the absence or either chemotherapy or radiotherapy. However, Evens (29)

observed complete remission in only three of eight patients who received rituximab monotherapy for PCNSL; responses were limited to patients with early PTLD. Recently Dugan (199) reported an overall response rate of 92% and an overall two year survival of 76.9% in 13 adult patients with PCNSL after transplant who failed or were ineligible for treatment with high dose methotrexate or WBRT when treated with a regimen that included induction therapy with dexamethasone and rituximab as well as antivirals ganciclovir/valganciclovir and zidovudine; antivirals were continued for a median of 26.5 months. Over the past decade there has been an increasing number of additional case reports in transplant recipients with PCNSL achieving complete re-mission using either standard or escalating doses of rituximab alone (reviewed by 200). Induction and consolidation regimens used in immunocompetent patients with PCNSL should be considered as first line treatment in transplant patients with CNS PTLD who are able to tolerate therapy. In patients who are ineligible for this treatment and in stable patients with disease early after transplant systemic rituximab therapy along with RIS and antiviral therapy might be considered as an initial therapeutic strategy.

Use of viral load to monitor response to PTLD therapy and predict relapse: Although data are limited, patients with EBV + PTLD as well as those receiving preemptive therapy, high viral loads often fall and sometimes clear in peripheral blood in the short term, coincident with clinical and histologic regression in response to interventions that include reduction of immunosuppression and adoptive immunotherapy (187, 201). In contrast, some clinicians have observed that when rituximab is used, viral load measured in cellular blood components fell dramatically and remained low even in the face of progressive disease and relapse (202-204).

In pediatric patients, particularly those experiencing primary infection after transplant, asymptomatic intermittent or persistent viral load rebound occurs frequently with no short-term consequences. Adult PTLD patients have been observed to relapse in the presence of persistently low viral load (203). However, recent data suggest that the sample type may influence the usefulness of viral load testing as plasma monitoring appears to correlate better with treatment response and relapse than monitoring in the cellular compartment (204, 205). In a recent study Kanarky (76) found that measurement of EBV DNA in either plasma or peripheral blood mononuclear cells could differentiate between untreated cases EBV+PTLD, EBV+PTLD in remission and untreated EBV- PTLD but plasma was a more reliable marker in the separation of these three groups. However, individual patients were not serially monitored in this study. Further studies correlating serial monitoring in different sample types to individual PTLD patient outcomes is required to confirm the optimal specimen type that should be used for this purpose.

Prognostic Indicators of PTLD: Outcomes for patients with CD20+ PTLD have improved as evidenced by recent adult (163,164) and pediatric phase II clinical trials (184,185), likely as the result of the availability of rituximab and improved management of both immunosuppression and infection during treatment. Although several prognostic factors/ indices have recently been proposed by investigators, several studies spanned the pre and post rituximab era and involved non-standardized approaches to treatment (206, 207) or were single center studies that involved relatively small number of patients in the post-rituximab era (207,208). The largest study in the post –rituximab era involved 500 PTLD cases in kidney transplant

recipients in a French registry proposed a prognostic score that included age, creatinine, lactate dehydrogenase level, disease localization and histologic features (209). Although this score was validated in a smaller single center study, it did not appear to be superior to the International Prognostic Index (IPI) used in immunocompetent lymphoma patients which includes the variables age, performance status, stage, lactate dehydrogenase level and number of extranodal sites (210). In both large recent prospective phase II treatment trials of CD20+ PTLD in adults (163,164) only response to rituximab and IPI (<3 or >3) influenced overall survival. There was no difference in overall response rate between EBV-negative and EBV-positive PTLD in these trials (163, 164) confirming the results of a recently reported single center experience (27). Patients with T cell PTLD (206,207) and PCNSL (30) appear to have a poorer prognosis than other PTLD patients.

Treatment recommendations:

1. We recommend RIS to the lowest tolerated level as initial therapy for nearly all early and late B cell PTLD in patients who do not have rapidly progressive disease **(strong/moderate).** This approach has not been validated for some pathologic subtypes such as Burkitt and Hodgkin lymphoma. There are insufficient data to both prescribe protocols for immunosuppression reduction and make recommendations for or against switching to an mTOR inhibitor.

2. Antiviral therapy and/or IVIG alone should not be used for PTLD in the absence of other interventions (i.e., RIS, rituximab, chemotherapy) **(strong /very low)** There are insufficient data to recommend for or against their use as adjunctive therapy

3. We recommend rituximab monotherapy as the next level of treatment for adult and pediatric CD20+PTLD in patient with progressive disease after RIS **(adults: strong/ high, pediatric strong/moderate).** Treatment protocols for rituximab induction and consolidation regimens as outlined by the adult RSST trial (164) should be followed in both adults (**strong/low**) and children (**weak /very low**)

4. In patients able to tolerate therapy we recommend cytotoxic chemotherapy for CD20+ PTLD in patients who have progressive disease after rituximab induction therapy (adult: **strong/moderate**, pediatric: **strong/ very low).** The chemotherapy protocol used in the RSST trial (R-CHOP 21) is recommended for adults (**strong/ low).**

5. In children with EBV+ PTLD, the low-dose cyclosphophamide and prednisone regimen plus rituximab as outlined by Gross (185) is recommended (**strong/ very low**).

6. We recommend the chemotherapy regimens used in immunocompetent patients with the same diagnosis for patients with CD20- B cell (including plasmablastic, plasma cell myeloma / plasmacytoma-like PTLD), T cell PTLD, Hodgkin and Burkitt lymphoma (**weak/moderate**)

7. We recommend the chemotherapy regimens used to treat PCNSL in immunocompetent patients as outlined by Ferreri (196, 197) for treatment of CNS PTLD (**weak/low**). In patients unable to tolerate these regimens and those with disease occurring early after transplant, regimens that include systemic rituximab, dexamethasone and antivirals might be considered **(weak/very low)**

8. During treatment of PTLD using strategies other than RIS, infection prophylaxis should be reviewed; Prophylaxis for *Pneumocystis jirovecii* pneumonia should be reinstituted if it has been discontinued (**strong/high**)

9. The routine use of EBV viral load monitoring in peripheral blood to monitor treatment response to EBV+ PTLD is not recommended (**weak/very low**).

Retransplantation after PTLD

In an analysis of the UNOS database, no recurrent PTLD was reported among 69 patients (27 kidney, 22 liver, 9 lung, 6 heart, 4 intestine, 1 pancreas) who underwent repeat transplantation after an episode of PTLD, one third of which had recurred in the first post-transplant year with only 1.4% diagnosed beyond the first decade (211). The interval between PTLD and retransplantation was greater than 1 year in 75%. The majority were children at the time of first transplant, suggesting that many may have developed PTLD in the setting of a primary EBV infection. In a similar French registry study of 52 kidney transplant recipients who underwent 55 retransplantations at a median of 90 months (range 28-224 months) after an initial PTLD event, only one case of PTLD occurred after retransplantation (212). Although the optimal time from PTLD remission to retransplantation is unknown, these studies suggest that retransplantation is appropriate as long as patients have remained disease-free for a significant interval and an immune response to the initial EBV infection has occurred. In the setting of liver, heart, and lung transplantation, timing is largely dictated by clinical need. At present, no data suggest that any one immunosuppressive protocol is superior to another in this setting. In general, there is a trend to avoid induction with anti-thymocyte preparations.

Recommendation (re-transplantation)

1. We recommend re-transplantation in patients with complete remission after PTLD when clinically indicated provided patients have remained disease free for a significant interval and in the case of early EBV+ PTLD associated with primary EBV infection, there is evidence for the development of an adaptive immune response such as seroconversion (**strong/moderate**)

Research Priorities

Epidemiology and Risk Factors

- Ongoing studies of epidemiologic trends and risk factors for PTLD in both adult and pediatric SOT populations should be undertaken. EBV+ PTLD (occurring early versus late after transplant /stratified by morphologic subtype) and EBV negative PTLD should be evaluated as possible distinct and independent endpoints.

Diagnostic and Evaluative Testing

- Ongoing validation of the impact of WHO IS and other standardization efforts on result harmonization across commonly used commercial assays using clinical plasma and whole blood samples.
- Further studies comparing plasma and whole blood EBV testing results in specific clinical settings that include post-transplant surveillance, PTLD diagnosis and treatment monitoring. Results in SOT recipients and HSCT should be analyzed separately.
- Multicenter studies relating molecular and other ancillary pathologic studies (see above) to patient outcomes.
- Studies of EBV transmission to seronegative recipients by seropositive donors

< 6 months of age should be undertaken since there is evidence to suggest that young infants are protected from EBV infection by maternal antibody during this period.

Clinical Staging

- Validation of the utility of PET-CT/MRI for PTLD staging and treatment response assessment and follow up monitoring.

Prevention

- Multicenter randomized controlled trial of valganclovir prophylaxis versus no prophylaxis in EBV mismatched patients not receiving this agent for CMV prophylaxis; the use of viral load detection (including timing in relationship to prophylaxis), peak viral load, set-point viral load, time to clearance of viral load as surrogate PTLD risk end points should be explored.
- Multicenter randomized controlled trial comparing addition of rituximab versus no change in EBV mismatched patients with ongoing rises in viral load or persistent elevated viral loads despite RIS.
- Studies of the biology and natural history of CVLP and allograft specific PTLD risks.
- Clinical trial to examine whether antiviral treatment of the donor or pre-transplant treatment of recipient with antivirals or rituximab impacts EBV transmission.

Treatment

- Phase II clinical trial evaluating RSST in children with PTLD.
- Multicenter randomized clinical trial comparing adoptive immunotherapy with cytotoxic chemotherapy in patients with EBV+ PTLD failing rituximab therapy.

- Registry to allow comparison of outcomes of patients given different treatment modalities in patients with CD20-negative PTLD, T cell PTLD, Burkitt and Hodgkin lymphoma and CNS lymphoma.
- Enhanced pathology studies of PTLD biopsies in clinical trial setting to include studies of genetic mutations, infiltrating T cell, immune invasion markers, and viral and cellular genome expression in order to develop biomarkers that might predict treatment response.

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