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Post-Transplant Lymphoproliferative Disease (PTLD): Risk Factors, Diagnosis, and Current Treatment Strategies

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Abstract

Post-transplant lymphoproliferative diseases (PTLD) are heterogeneous lymphoid disorders ranging from indolent polyclonal proliferations to aggressive lymphomas that complicate solid organ or hematopoietic transplantation. Risk factors have been identified, including viral infections, degree of immunosuppression, recipient age and race, allograft type, and host genetic variations. Clinically, extra-nodal disease is common, with 10–15 % presenting with central nervous system (CNS) disease. Most PTLD cases are B cell (5–10 % T/NK cell or Hodgkin lymphoma), while approximately one-third are EBV-negative. World Health Organization (WHO) diagnostic categories are: early lesions, polymorphic, and monomorphic PTLD; although in practice, a clear separation is not always possible. Therapeutically, reduction in immunosuppression remains a mainstay, and recent data has documented the importance of rituximab +/− combination chemotherapy. Therapy for primary CNS PTLD should be managed according to immunocompetent CNS paradigms. Finally, novel treatment strategies for PTLD have emerged, including adoptive immunotherapy and rational targeted therapeutics (e.g., targeting downstream signaling pathways of virus-encoded latent membrane protein-2A).

Keywords

Post-transplant lymphoproliferative disease; PTLD; Lymphoma; Non-Hodgkin lymphoma; Hodgkin lymphoma; Central nervous system; CNS; Lymphoma; Epidemiology; Risk factors; Diagnosis; Pathogenesis; Genetic variation; EBV; LMP2A; Prognosis; Treatment; Rituximab; Adoptive immunotherapy; Chemotherapy

Introduction

Post-transplant lymphoproliferative disease (PTLD) is a heterogeneous clinical and pathologic group of lymphoid disorders ranging from indolent polyclonal proliferation to aggressive lymphomas that may complicate solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). The first cases were in renal transplant

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recipients in 1968 by Doak et al. [1], and the term PTLD was first introduced in 1984 by Starzl et al. [2].

The incidence of PTLD in HSCT without T cell depletion is 0.5–1 % [3, 4], while the risk is increased 50–120 % in SOT recipients compared with the general population [5]. The highest risk of SOT-related PTLD occurs among heart, lung, intestinal and multi-organ transplant subjects, reaching an absolute risk of 25 % in some series [5–7], while the risk is lower (1–5 %) in renal and liver transplant recipients [5, 8, 9]. Historically, mortality rates in SOT-related PTLD were 50–70 % [7, 10–12] and up to 70–90 % in HSCT [3], although recent data suggests that outcomes have significantly improved [13•, 14••].

Reduction of immunosuppression (RI) has been a mainstay in the therapeutic approach of PTLD for several decades [2]. Responses to RI, however, are observed in less than half of patients and remissions are often not durable [11, 15, 16, 17•]. Therapy in addition to RI includes rituximab and chemotherapy, given together or in sequence [13•, 14••, 18, 19]. In addition, there are several novel therapeutic approaches being investigated. We review herein risk factors, pathological classification, clinical presentation, and current and future treatment modalities for PTLD.

Risk Factors

Several risk factors have been shown to increase the risk of PTLD; these include infection, degree and duration of immunosuppression, age and race of recipient, type of allograft, and genetic factors.

Infectious Etiologies

The majority of PTLDs (55–65 %) are associated with EBV infection [20–25]. In immunocompetent hosts, the EBV genome is immortalized, forming an episome in latently infected B cells [18]. Immunosuppression leads to depressed T cell function with associated lack of T cell control of B cell proliferation; this results in uncontrolled proliferation of EBV-transformed B cells, which contributes to the development of PTLD. The risk of PTLD is increased when an EBV(−) patient receives a transplant graft from an EBV(+) donor [24–26]. McDonald et al. reported that EBV seronegative subjects had a 4.7-fold higher relative hazard ratio compared with EBV(+) subjects (P=0.02). Furthermore, among EBV donor(+)/recipient(−) subjects, the relative hazard ratio was increased six-fold (P=0.0001) [26].

Data evaluating the predictive value of host serum EBV and risk of PTLD have shown mixed results [27, 28]. The American Society of Transplantation recommends checking monthly EBV viral load for 1 year in EBV(−) patients following SOT [28]. Of note, there is data showing the importance of performing EBV testing in the cellular blood compartment (i.e., whole blood) [29]. Rising EBV viral titers should raise the suspicion for EBV-related PTLD; however, diagnosis must be confirmed by biopsy.

Mismatch for CMV, such as when seronegative recipient receives an organ from seropositive donor, was shown to be associated with a seven-fold increase in PTLD. Hepatitis C virus

(HCV) and Human Herpes Virus-8 were also reported as risk factors, especially when they coincided with EBV infection [30–32].

Immunosuppression

PTLD has been reported to occur at a higher rate (8–25 %) in heart, lung, intestinal, and multi-organ transplants, owing in part to the degree of immunosuppression warranted in these cases [5–7], whereas the incidence rate is 1 – 5 % in kidney and liver transplants where lower doses and duration of immunosuppression are utilized. There is additional evidence that the type of RI may impact risk. PTLD was described initially in the pre-cyclosporine era suggesting that any immunosuppressive agent that blunts cellular immunity constitutes a risk factor [6]; however, data regarding the role of individual drugs is conflicting [18, 33]. Anti-thymocyte globulin (ATG), calcineurin inhibitors, anti-CD3 (OKT3), tacrolimus, and cyclosporine have been individual agents implicated as potential risk factors for PTLD [5, 7, 33, 34].

HSCT-Related Factors

The primary factor in the development of PTLD in HSCT recipients is T cell depletion (TCD) [6, 35]. Other factors include HLA mismatch, unrelated donor transplant, severity of Graft-versus-host disease (GVHD), and transplant for immunodeficiency disorders [3, 4, 18, 36]. Bhatia et al. reported that ATG and busulfan, commonly used in HSCT, are risk factors for PTLD with a relative risk of 9.4 and 2.19, respectively [3]. In the same study, they noted a 65 % increased risk of PTLD when patients had TCD HLA mismatched transplant for a primary immunodeficiency disorder.

Age and Race

Opelz et al. reported that SOT subjects ages < 10 and > 60 years were at increased risk of PTLD [7]. Younger patients are at increased risk due to frequently being EBV(−) at time of transplant [7, 22], and their predisposition to primary EBV and CMV infections early in the post-transplant course [37]. In contrast, older recipient age is likely related in part to decreased immune surveillance in this population [6, 7, 18]. Additionally, higher incidence or PTLD has been reported in White (renal) transplant patients compared with Blacks, irrespective of recipient EBV serostatus [33, 38]. Pre-transplant malignancy has also been described as a potential factor for the development of PTLD [34, 38].

Genetic Factors

Host genetic variation has been identified as a factor in the development of PTLD. Polymorphisms in cytokine genes, including interleukin-10 (IL-10), interleukin-6 (IL-6), and interferon-gamma (IFN-α) may influence the predisposition to PTLD [6]. Other data have shown that IFN-α promoter +874A/A, a genotype associated with low IFN-α secretion, correlated with increased risk of early PTLD [39, 40]. In contrast, there was no correlation between IFN-α promoter +874A/A and late-onset PTLD [41]. Other candidate genes implicated in the pathogenesis of PTLD include polymorphisms at donor and recipient human leukocyte antigens (HLA) A26 and B38 haplotypes, whereas donor haplotypes HLA-A1, HLA-B8 and HLA-DR3 were identified as *protective factors* [42]. Other series

identified an increased risk of PTLD with recipient HLA-A2, HLA-A11, HLA-B5, HLA-B18, HLA-B21 and HLA-B35, and decreased risk with HLA-A03 and HLA-DR7 [43, 44]. Bakker et al. reported recipient-donor mismatching at HLA-B locus alone to be associated with PTLD after renal transplant [45]. Other candidate genes include TGF-(31 and variant alleles in TNF-α promoter and TNF-α receptor-1 promoter region [41, 46]. These genetic data may prove useful for the assessment of PTLD risk and ultimately in the development of novel preventive strategies.

Pathologic Classification

Most PTLD cases are B cell, with only 5 % of cases being of T cell or T/NK cell origin. Approximately 60–70 % of B cell PTLDs are EBV-related, while < 10–15 % of the T cell cases are EBV-related [47]. Based on criteria delineated in the 2008 World Health Organization (WHO) Classification, PTLDs can be sub-classified into four categories based on morphologic, immunophenotypic, and molecular criteria (Table 1) [48]. In practice, a clear separation between the different WHO categories of PTLD is not always feasible, and early lesions, polymorphic, and monomorphic PTLD likely represent a pathological spectrum [49]. This underscores the importance of expert pathologic evaluation of suspected PTLD.

Early Lesions

Early lesions, which include lesions with features of infectious mononucleosis (IM) and plasmacytic hyperplasia, show preservation of original tissue architecture [48, 50]. The name implies that these lesions show the first morphologic changes in the spectrum of PTLDs. These lesions may occur at any time following SOT or HSCT [48, 51], and are more frequent in patients EBV(−) prior to transplant [48, 50, 52]. These lesions are composed of a mixed cell population consisting primarily of small lymphocytes with scattered plasma cells and immunoblasts, that exhibit minimal, if any, cytologic atypia. Some IM-like PTLD lesions exhibit small clonal or oligoclonal B cell populations. EBV small terminal repeat genome analysis is typically polyclonal, but it may rarely have a monoclonal pattern [53•].

In a recent analysis by Nelson et al., early PTLD cases were shown to develop later than previously reported (median time from transplant 50 months), involved mostly tonsils and adenoids, were EBV(+), and showed increased pS6 expression, which is a downstream effecter of mammalian target of rapamycin (mTOR) [51]. The same study reported excellent clinical response with RI alone.

Polymorphic PTLD

This type is composed of “polymorphic” cell populations, including small and medium-sized lymphocytes, atypical immunoblasts, mature plasma cells and Reed-Sternberg (RS)-like cells. The infiltrate causes effacement and destruction of the underlying tissue architecture and may show malignant features, such as nuclear atypia, necrosis, and a high mitotic rate [53•]. Lesions are mostly monoclonal, and a small proportion (15 %) reveals clonal cytogenetic abnormalities [54]. This is the most common subtype in the pediatric age group, and is mostly related to primary EBV infection [55].

Monomorphic PTLD

These lesions are composed of a population of large lymphocytes and plasma cells with a uniform appearance, and are further subdivided into B cell and T cell neoplasms. Although T cell or T/NK monomorphic PTLDs occur, the vast majority are of B cell origin, and have detectable EBV genome and clonal rearrangement of Ig genes [18, 53•]. Approximately 70 % of these lesions were reported to have cytogenetic abnormalities, including trisomy 9 and 11 or both, loss of 17p, and rearrangement of 8q24 (*MYC*) [54].

Hodgkin Lymphoma (HL)

HL is a rare form of PTLD, and when present, it primarily occurs in renal transplant recipients. Features are similar to HL in normal subjects, while most cases are EBV(+) [18]. Biopsy shows RS cells and variants on a mixed background of small lymphocytes, histiocytes and esosinophils [53•]. The Hodgkin cells exhibit a classical phenotype CD15+, CD30+, dim PAX5+, CD3- and CD45- [18]. CD20 may be negative or show weak and/or heterogeneous positivity [18, 48, 53•]. Caution should be taken when RS cells are seen, as RS cells can also be found in polymorphic and IM-like PTLD, in which EBV-infected cells may show RS-like features, but lack CD15 expression and are usually CD20+ and CD45+ [53•].

EBV(−) PTLD

Approximately 30–45 % of PTLD cases are EBV(−). They are typically diagnosed later, occurring at a median time from SOT at 62 months versus 11.5 months for EBV(+) cases [13•, 18, 56, 57]. Additionally, EBV(−) PTLD have been shown to be more frequently monomorphic compared with EBV(+) disease (67 % vs. 42 %, respectively) [57]. Johnson et al. reported increased expression of BCL-6, decreased MUM-1/IRF4+ and less frequent non-germinal center phenotype in EBV(−) versus EBV(+) PTLD [18, 22]. It was previously reported that EBV(−) PTLD are associated with worse prognosis compared to EBV(+) disease [56, 57]; however, recent data does not support this [11, 13•, 17•, 58, 59].

Clinical Presentation

Lymphadenopathy is often absent, and symptoms are usually due to interference with the function of involved organs. Classic B symptoms such as pyrexia, sweats, and weight loss can occur [12]. Clinical features of PTLD are often non-specific, while extranodal involvement is common, including gastrointestinal tract (GIT), lungs, skin, bone marrow (BM), and central nervous system (CNS) [10, 11, 13•, 18, 59, 60]. Rarely, BM involvement can be the only disease site [53•]. PTLD typically has a more rapid onset in HSCT patients, with median time of 4–6 months after transplant [3, 4, 23].

PTLD has been reported to involve the transplanted organ in heart, lung, and liver transplants in approximately half of cases, whereas the GIT was the most commonly involved site in renal transplant recipients [7]. CNS disease is present in approximately 10–15 % of all PTLD cases [61–65], of which most are primary CNS lymphoma. Robson et al. reported that CNS involvement might be decreasing with alteration in immunosuppressive

regimens [66]. In HSCT subjects, PTLD often has a more aggressive course that presents with widely disseminated disease and multi-organ involvement [18].

Treatment

The primary goal in the treatment of PTLD is cure, and a concomitant objective should be preservation of the allografted organ. Due In part to the clinicopathologic heterogeneity of the disease (e.g., graft type, risk of rejection, comorbidities, disease presentation, tumor burden, etc.), there is not a unified treatment approach. However, several treatment paradigms have emerged. Since the first report of PTLD, the mainstay of treatment has been RI [2, 13•, 18], although as noted before, responses occur in only half of patients and durable remissions are not common [11, 16, 17•]. Other treatment options include rituximab monoclonal antibody given combined or in sequence with combination chemotherapy, while surgery or radiation may be considered in select cases. Additionally, novel therapeutic approaches continued to be explored, including adoptive immunotherapy, cytokine treatment, and anti-EBV-based therapy (Table 2).

Reduction of Immunosuppression (RI)

RI has been a mainstay of PTLD treatment since the disease was first recognized more than 40 years ago [1, 67]. Objective tumor responses to RI, however, are highly variable, ranging from 0–73 % [15, 16, 17•, 18, 34]. Further, in most series, durable responses are maintained in < 10–20 % of cases [11, 16, 17•, 21, 58, 59]. Two additional concerns with RI are the relatively long median time to initial response (i.e., 3– 5 weeks) and the risk of graft rejection/organ failure [34], although the latter has not been adequately documented in many PTLD series [18]. There remains a critical need to accurately identify patient populations whereby RI alone will be safe and effective.

Factors that have been shown to predict poor outcomes with RI include increased LDH, multi-organ involvement/dysfunction, late-onset PTLD, older age (> 50 years), and presence of B symptoms [16, 34]. Reshef et al. recently showed that multi-organ involvement did not correlate with response to RI [68•]. The study included 148 SOT-related PTLD cases; overall response rate (ORR) to RI was 45 % (37 % complete remission [CR]). However, 40 % of patients developed acute graft rejection. Interestingly, there was no correlation between degree of RI and incidence of graft rejection. This study also found that BM or liver involvement and HCV infection predicted poor response to RI. The 3-year overall survival (OS) for all patients was 55 %, while it was 100 % without risk factors versus 8 % for patients with two or more risk factors.

Altogether, evidence supports continued use of RI as initial therapy for most PTLD patients with the degree of reduction (e.g., typically 50–75 %) dependent on individual patient factors (e.g., risk of graft rejection, type of SOT, etc.). However, it should be highlighted that RI may be insufficient as a single therapeutic modality, especially for patients with multi-organ dysfunction, high disease burden and/or aggressive clinical disease in need of immediate therapeutic response.

Rituximab

Prior to 2005, 3-year OS rates ranged from 30–50 % in most PTLD series [7, 10–12, 15, 57, 69, 70]. Recent data has strongly suggested that outcomes for PTLD have improved in the post-rituximab era [13•, 14••]. In the mid-2000s, data emerged showing rituximab was efficacious for PTLD after failure from RI or other treatments [15, 58, 71– 73]. Choquet et al. conducted the first prospective (phase II) trial of single-agent rituximab in SOT-related PTLD after failure of RI [71]. The ORR was 34 %, EFS 72 %, and 1-year OS was 67 %. Elevated LDH was associated with poor response and number of affected sites correlated inversely with survival. Gonzalez-Barca et al. evaluated extended rituximab dosing administering a second 4-week course of rituximab for patients who did not achieve CR with the first course; the intent-to-treat CR rate was 61 % [74]. At 28 months, EFS and OS were 42 % and 47 %, respectively. Elstrom et al. reported an ORR of 68 % (CR 59 %) with rituximab-based therapy with median OS of 31 months [58]. Additionally, Ghobrial et al. documented that ORR and median OS appeared superior in PTLD patients treated with rituximab compared with those who received other treatment [15].

Two recently published studies showed that early introduction of rituximab in PTLD treatment appeared to improve outcomes [13•, 14••]. In a retrospective, population-based, multicenter analysis of 80 SOT-related PTLD patients, Evens et al. reported that patients who received frontline rituximab-based therapy achieved a 3-year PFS and OS of 70 % and 73 % respectively, compared with 21 % and 33 % for those who did not [13•] (Fig. 1). Further, they identified a novel survival model; on multivariate regression analysis, three factors were associated with inferior OS: CNS involvement, bone marrow involvement, and hypoalbuminemia [13•]. A survival model based on number of these adverse factors present (i.e., 0, 1, or 2) was formed: 3-year PFS rates were 84 %, 66 %, 7 %, respectively, and 3-year OS rates were 93 %, 68 %, 11 %, respectively. The model remained highly predictive when only including bone marrow involvement and hypoalbuminemia.

In the largest prospective PTLD trial conducted to date, Trappe et al. examined the response to a 4-week course of rituximab followed by CHOP (cyclophosphamide, doxorubicin, oncovin, prednisone) given as sequential treatment (ST) to 74 SOT-related PTLD subjects [14••]. In the initial study design, patients received 4-week course of rituximab immediately followed by four sequential cycles of R-CHOP. After an interim analysis showed that response to rituximab correlated with OS (p= 0.007) and that the TRM rate was 9 % with ST, the trial was modified. Patients who achieved complete remission (CR) with the initial course of rituximab received a second 4-week course of single-agent rituximab (known as risk stratified sequential therapy, RSST). Patients who did not achieve CR with initial rituximab therapy received four cycles of R-CHOP. The ORR in ST and RSST were 89 % and 90 %, respectively, with CR rates of 69 and 73 %, respectively. At 1 year, progression-free survival (PFS) was 86 % and 90 % in the ST and RSST groups, respectively. Results of the ST portion of the clinical trial have recently been published [14••].

Chemotherapy

Several chemotherapeutic regimens have been used in the treatment of PTLD, with CHOP (cyclophosphamide, doxorubicin, oncovin, prednisone) being the most common [16, 59, 75–

77]. CR rates with combination chemotherapy for PTLD are up to 92 %, although enthusiasm has been tempered due to treatment-related toxicity, in particular infectious-related complications. Moreover, rates of treatment-related mortality (TRM) have been noted in several series (i.e., 13–50 %) [18]. Choquet et al. used CHOP for 26 SOT-related PTLD subjects [78]. The CR rate was 50 % and 5-year and 10-year PFS were 43 % and 32 %, respectively; however, TRM was 31 %. Additionally, Evens et al. noted that the use of chemotherapy (versus no chemotherapy) was associated with an increased risk of SOT rejection [13•]. Nevertheless, combination chemotherapy remains an important component of the treatment paradigm for PTLD. It should likely be utilized, however, in more towards a RSST strategy as proposed by Trappe et al. Furthermore, intensive supportive care should be implemented, including use of growth factors, prophylactic antibiotics, and there should be consideration for further decrease (or discontinuation) of immune suppressant therapy during chemotherapy.

Local Therapy

Local therapies such as surgery and radiation may be beneficial for select, localized PTLD cases (newly-diagnosed or relapsed) [79]. Local therapy is typically done in conjunction with RI.

Immunotherapy

An important factor in the pathogenesis of PTLD is the compromised cytotoxic T cell response secondary to immune suppression in transplant recipients. Nalesnik et al. reported favorable response to immunotherapy with autologous lymphocyte-activated killer cells in EBV(+) and EBV(−) PTLD patients [80]. Donor-derived EBV-specific cytotoxic T-lymphocyte (CTL) infusions have also been utilized for treatment of PTLD in HSCT subjects [81–84]. CTL was used as a prophylactic modality with favorable response in subjects with rising EBV titers in both adult and pediatric populations [84, 85]. Additionally, Haque et al. reported that CTL therapy was associated with an ORR of 64 %, CR 36 %, and 6-month OS of 79 % when given to SOT and HSCT-related PTLD patients [83]. Minimal data are available regarding use of autologous or allogeneic HSCT for relapsed/refractory PTLD, although case reports have demonstrated its feasibility in select cases.

Antiviral Therapy

Antiviral agents have been used for prophylaxis and therapy in of EBV-related PTLD. In several series, ganciclovir and acyclovir were used for prophylaxis, with reported risk reduction ranging between 38 and 44 % [80, 81]. The benefit was more prominent when EBV prophylaxis was given in the first year post-transplant. These data are intriguing, although they warrant validation in prospective, randomized clinical trials. Use of antiviral agents for *primary treatment* of PTLD is lacking and further studies are needed. In vivo, these anti-viral agents are ineffective against EBV, since they do not eradicate latently infected B cells as EBV survives as an episome outside of the lymphocytes genome. A therapeutic approach to harness anti-viral therapy involves use of arginine butyrate, in order to up regulate thymidine kinase, which is subsequently followed by ganciclovir therapy [86]. Continued study of this concept is needed.

Novel Therapies

New treatment modalities that have been explored include IL-6 and IL-10 monoclonal antibodies, and IFN-α [87–92]. Additionally, approximately 70–80 % of PTLDs express CD30 [93]; CD30-directed therapy, such as with the recently approved antibody drug conjugate brentuximab vedotin, is being studied in CD30(+) and/or EBV(+) lymphoid malignancies (NCT01805037). As mentioned previously, there is data regarding increased expression of pS6 ribosomal protein, a downstream effecter of mTOR [51]. The mTOR inhibitor, sirolimus (rapamycin), has been shown to have antiproliferative properties in lymphoid tumor models including pre-clinical data in PTLD cell lines [94]. Whether sirolimus, or other newer mTOR inhibitors, have clinical efficacy in PTLD is uncertain and needs further investigation. Clinical investigation of this pathway will be particularly important, since there is data that showed maintenance therapy with an mTOR inhibitor was associated with an increased risk of PTLD compared with non-mTOR maintenance therapy [95].

Latent EBV infection is characterized by the expression of multiple viral genes; three of these are the integral membrane proteins, latent membrane protein-1 (LMP1), LMP2A and LMP2B. LMP2A has been shown to have dramatic effects on normal B cell receptor (BCR) signal transduction, including Bruton's tyrosine kinase (Btk) and spleen tyrosine kinase (Syk) [96]. LMP2A not only blocks BCR signal transduction, but also provides a BCR-like signal that propagates B cell development and survival in the absence of normal BCR signals [97••]. In addition, LMP2A constitutively activates other downstream signaling pathways, such as NF-kB, Abl, MEK/ERK, AKT, and mTOR [98]. LMP2A cannot be directly targeted, although an intriguing approach may be to block LMP2A–specific function in order to eradicate latent EBV infection by utilizing specific pharmacologic inhibitors of its downstream pathways.

CNS PTLD

CNS PTLD warrants special attention in part due to its unique presentation and distinctive warranted therapy. When present, CNS involvement has been shown to be predictive of inferior survival in PTLD series [2, 6, 7, 15, 16]. Through an international retrospective analysis, we recently described 84 PCNS PTLD patients treated over a 14-year period in the post-rituximab era [99•]. The median time of SOT to CNS PTLD was 54 months, 79 % of patients had kidney SOT, and 83 % of cases were monomorphic. Despite most cases (83 %) occurring "late" (i.e., > 1 year after SOT), tumor was EBV(+) in 94 % of cases. Additionally, multifocal presentation was common and one-third had deep brain involvement.

Optimal therapy for PCNS-PTLD is not known, although use of RI alone is typically not advocated since this approach requires several weeks to take effect; these patients are often in need of a more urgent therapeutic response. Recent series have suggested treatment paradigms similar to immunocompetent primary CNS lymphoma (e.g., high-dose methotrexate-based (HD-MTX) therapy) [99•, 100]. Taj et al. reported that HD-MTX was safe and effective in the treatment of PCNS-PTLD in pediatric liver transplant recipients [100]. In our series, outcomes for PCNS PTLD were overall modest, although

approximately 40 % of subjects achieved long-term survival [99•]. Use of HD-MTX and high-dose cytarabine appeared important, while the impact of rituximab was not clearly established.

Conclusion

There has been an increased understanding of the biologic and molecular pathogenesis of PTLD in recent years that has resulted in refined therapeutic approaches and improved outcomes for this heterogeneous disease. A number of risk factors have been elucidated over the past decade; prospective validation and combinatorial analyses of these factors are needed in order to enrich the prediction of PTLD development. At diagnosis, expert pathologic review is essential, including identification of the WHO subtype. For treatment, we recommend RI alone for most cases of 'early' PTLD. For polymorphic or B cell monomorphic PTLD, rituximab together with RI can be used for most cases, with combination chemotherapy reserved for non-responding (and T cell or HL) cases. Continued research is needed to identify patient subsets in these cases whereby RI alone may be effective. Treatment for CNS PTLD should be approached using similar therapeutic paradigms as for immunocompetent CNS lymphoma. Finally, novel treatment approaches, such as adoptive immunotherapy and other rational targeted therapeutics, should continue to be explored.

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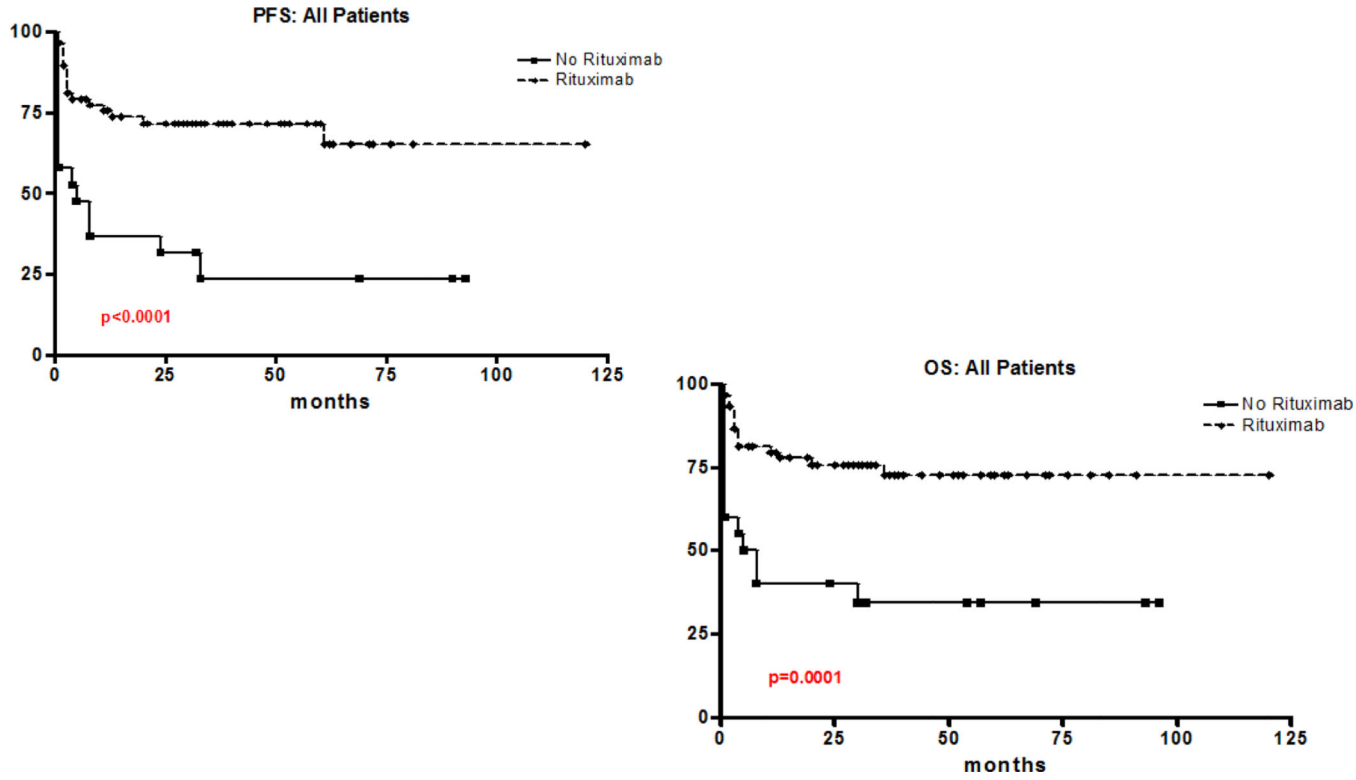

Fig. 1. Rituximab-related progression-free survival (PFS) and overall survival (OS)

Kaplan-Meier curves of PFS and OS in PTLD patients who received rituximab-based therapy compared with patients who did not receive rituximab as a component of initial therapy was associated with significantly improved PFS ($P < 0.0001$) and OS ($P = 0.0001$) for the former cohort. Modified from original figure; [13•]. Reprinted with permission.

Table 1

WHO Classification of PTLD (2008)

Category	Morphology	Clonality
Early lesions • Plasmacytic hyperplasia • Infectious mononucleosis-like lesions	Architecture intact; admixture of small polyclonal B and T cell immunoblasts and plasma cells; typically EBV(+)	Rare; small clonal or oligoclonal populations may be apparent
Polymorphic PTLD	Architecture effaced; full spectrum of lymphoid maturation (immunoblasts, plasma cells and small to medium B cell and T cell lymphocytes); often EBV(+)	Clonal Ig genes typically found and non-clonal T cells
Monomorphic PTLD [*] • B cell neoplasms DLBCL Burkitt lymphoma Plasma cell myeloma Plasmacytoma-like lesions Other[^] • T cell neoplasms Peripheral T cell lymphoma NOS Hepatosplenic lymphoma Other	Architecture effaced; fulfills WHO criteria for plasma cell neoplasm or NHL (other than indolent subtypes[^]); phenotype dependent on subtype of NHL; EBV variably positive	Clonal B cells and/or clonal T cells present in virtually all cases
Classical HL-type PTLD	Architecture effaced; fulfills WHO criteria for classical HL	Not typically seen

[*] Classified according to the lymphoma they resemble

[^] Indolent B cell lymphomas arising in transplant patients are not classified as PTLD

WHO World Health Organization; *PTLD* post-transplant lymphoproliferative disease; *Ig* immunoglobulin; *EBV* Epstein-Barr Virus; *NHL* non-Hodgkin lymphoma; *HL* Hodgkin lymphoma; *DLBCL* diffuse large B-cell lymphoma; *NOS* not otherwise specified.

Table 2

PTLD Series: Treatment and Prognosis (minimum *N* = 40).

Author	*N*	Treatment	Outcome	Prognostic factors
Tsai et al. 2001 [79]	42	RI alone (71 %) RI + surgery (29 %)	Median RFS: 1.6 years Median OS: 2.8 years 3-year OS: 50 %	Elevated LDH Multi-organ involvement Age > 40 years
Leblond et al. 2001 [10]	61	RI alone in 89 %, then mixed	DFS with RI alone: 6 % Median OS: 24 months 3-year OS: 40 %	CNS involvement PS 2–4 Number sites > 1
Ghobrial et al. 2005 [11]	107	First-line therapy: RI alone (37 %), surgery +/− RI (24 %), chemotherapy +/− rituximab (8 %), radiation (7 %), none (14 %)	DFS with RI alone: 20 % Median OS: 32 months 4-year OS: 42 %	Monomorphic PS 3–4 Graft involvement
Maecker et al. 2007 [59]	55	100 % received RI; Additional therapy: chemotherapy alone (64 %), rituximab alone (12 %), rituximab + chemotherapy (10 %), none (12 %), autologous EBV T cells (2 %)	3-year OS: 72 %	BM involvement CNS involvement
Oton et al. 2008 [21]	84	First-line therapy: RI alone (61 %), chemotherapy +/− rituximab (11 %), surgery (10 %), antiviral (6 %), no therapy (11 %), and RT (1 %)	Median OS: 20.8 months	N/A
Knight et al. 2009 [17•]	78	Initial therapy: RI alone: 92 %; Subsequent therapy: chemotherapy (39 %), rituximab + chemotherapy (22 %), rituximab alone (10 %), none (10 %), surgery (8 %), other (11 %)	DFS with RI alone: 11 % Median OS: 8.2 years	Stage III-IV CNS involvement IPI 3–5
Evens et al. 2010 [13•]	80	100 % received RI; Additional first-line therapy: rituximab/chemotherapy (41 %), rituximab alone (34 %), chemotherapy (16 %), RI alone (9 %)	Median OS: not reached All patients: 3-year OS 62 % (rituximab-based: 3-year OS 73 %)	CNS involvement BM involvement Hypoalbuminemia
*Trappe et al. 2012 [14]	74	Initial therapy: 4-weeks rituximab; Subsequent: patients with CR after initial therapy (40 %)→ second 4-week course of rituximab, patients without CR (60 %) → R-CHOP x 4 cycles	Median OS: 6.6 years ORR: ST 89 %; RSST 90 % CR: ST 69 %; RSST 73 % 1-year PFS: ST 86 %; RSST 90 %	N/A

*Prospective study (all others are retrospective series)

N number; *RI* reduction in immunosuppression; *PS* performance status; *LDH* lactate dehydrogenase; *OS* overall survival; *PFS* progression-free survival; *DFS* disease-free survival; *RFS* relapse-free survival; *ORR* overall response rate; *CR* complete remission; *IPI* international prognostic index; *EBV* Epstein-Barr virus; *RSST* risk stratified sequential therapy; *ST* sequential therapy; *CNS* central nervous system; *BM* bone marrow; *R-CHOP* rituximab, cyclophosphamide, oncovin, prednisone; *N/A* not available.