13. Post-transplant Lymphoproliferative Disorder

Table of Contents

13.1 Overview of PTLD

Dharnidharka VR, Ruzinova MB, Marks LJ. (2024). Post-Transplant Lymphoproliferative Disorders (Review for Seminars in Nephrology). *Semin Nephrol*. Jan 2024;44(1). Retrieved from: https://www.sciencedirect.com/science/article/abs/pii/S0270929524000202

- A comprehensive review of PTLD with sections on pathogenesis, classification including new/proposed classification from World Health Organization (WHO) and International Consensus Classification (ICC), clinical features, diagnosis, prevention/pre-emptive treatment, treatment, and prognosis including a comparison of prognostic indexes.

Markouli M, Ullah F, Omar N, et al. (2022). Recent Advances in Adult Post-Transplant Lymphoproliferative Disorder. Cancers (Basel). Dec 1;14(23):5949. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36497432/

- A review of pathogenesis, clinical features, histologic classification, and risk factors of PTLD. Topics also include treatment and prevention, and novel therapies including tabelecleucel, antibody drug conjugates, and targeted therapies.

Abbas F, El Kossi M, Shaheen IS, Sharma A, Halawa A. (2020). Post-transplantation lymphoproliferative disorders: Current concepts and future therapeutic approaches. World J Transplant. 10(2), 29-46. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7093305/

- Comprehensive review of PTLD after solid-organ transplant and hematopoietic stem-cell transplant. Topics include epidemiology, risk factors, pathogenesis, clinical presentation, diagnosis and summary of treatment options.

Gandhi S, et al. (2020). Late-onset posttransplant lymphoproliferative disorders after solid organ transplantation in adults: a case series and review of the literature. Case Rep in Transplant. 2020, 1-9. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32095310/

- Case-series describing five late-onset PTLDs with rare histological features and multiorgan involvement.

Walti LN, et al. (2020). Association of antiviral prophylaxis and rituximab use with post-transplant lymphoproliferative disorders (PTLDs): A nationwide cohort study. Am J Transplant. EPub ahead of print. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33289340/

- Nationwide cohort study based on data from the multicenter nationwide observational Swiss Transplant Cohort Study (STCS) to describe the clinical characteristics of PTLD cases after SOT and to assess the effect of rituximab therapy and the use of antiviral prophylaxis on PTLD

occurrence. Total of 4765 SOT patients (7% kidney, 22% liver, 9% lung, 8% heart, 5% combined) with 57 cases of PTLD. 86% of PTLD cases were EBV positive. The overall PTLD incidence was 2.39 per 1000 person-years. Incidence rates for EBV+ PTLD at 1, 2, and 3 years post-transplant were 3.51, 2.24, and 1.75/1000 person-years and 0.44, 0.25, and 0.29/1000 person-year for EBV− PTLD. Majority of SOT patients receiving rituximab were kidney transplant recipients (95%). Among them, 88% received rituximab as induction therapy. The mean PTLD-free survival time at 9 years of follow-up was significantly shorter (0.104 years [95% CI 0.077–0.131]). Patients not receiving rituximab induction had a significantly shorter mean PTLD-free survival time at 9 years follow-up (0.067 years [95% CI 0.039–0.096]).

Romero S, et al. (2019). Post-transplant lymphoproliferative disorders after solid organ and hematopoietic stem cell transplantation. Leuk Lymphoma. 60(1), 142-150. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29966464/.

- Single center, retrospective study was conducted to compare the clinical, biological and histological features and outcomes of PTLD after solid organ transplant and hematopoietic stem cell transplant. Found that PTLD had an earlier onset in patients with allo-HSCT compared to SOT (4 vs 64 months, p<0.0001). Median overall survival after four years was 32% (95% CI, 22-48) in SOT and 10% (95% CI, 2-49) in allo-HSCT recipients, p = 0.002.

DeStefano CB, et al. (2018). Management of post-transplant lymphoproliferative disorders. Br J Haematol. 182(3), 330-343. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29741774

- Comprehensive review of PTLD following solid organ transplant and hematopoietic stem cell transplant with a focus on management. Includes an overview of ongoing clinical trials of novel agents

Dierickx D, Habermann TM. (2018). Post-Transplantation Lymphoproliferative Disorders in Adults. N Engl J Med. 378(6), 549-562. Retrieved from: http://www.nejm.org/doi/full/10.1056/NEJMra1702693

- A comprehensive review of PTLD in adult transplant recipients, including solid organ transplant and bone marrow transplant.

Dharnidharka VR. (2018). Comprehensive review of post–organ transplant hematologic cancers. Am J Transplant. 18(3), 537-549. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29178667

- Comprehensive review of hematologic cancers, including PTLD, following solid organ transplant.

Peters AC, et al. (2018). The changing epidemiology of posttransplant lymphoproliferative disorder in adult solid organ transplant recipients over 30 years: A single center experience. Transplantation, 102(9), 1553-1562. Retrieved from: https://journals.lww.com/transplantjournal/Fulltext/2018/09000/The_Changing_Epidemiology_of_Posttransplant.31.aspx?WT.mc.

- Single center study from Alberta evaluating SOT patients of all organs between 1/1/1984 - 12/31/2013 (n=4171) and the characteristics of those who developed PTLD. Multi-organ, small bowel, and thoracic transplants had an increased risk of PTLD (Multi-organ/small bowel: 95% CI 1.5-84; P=0.019; thoracic: 95% CI 1.5-4.5; P<0.001). Epstein-Barr virus seronegative patients had an eight-fold higher risk of PTLD (95% CI: 5.1-13; P<0.001). The risk for PTLD is higher at 1 year post-transplant vs. 10 years post-transplant (HR: 17.1, 95% CI: 8.1 - 35.7 versus HR: 11.5, 95% CI: 7 – 18.8).

Ghobrial IM, et al. (2005). Differences between early and late posttransplant lymphoproliferative disorders in solid organ transplant patients: are they two different diseases? Transplantation, 79(2), 244-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=15665775

- Retrospective review of SOT patients diagnosed with PTLD at a single U.S. center between December 1970 and May 2003. Early PTLD was defined as PTLD that occurs within 1 year post transplant. The authors concluded that patients with early PTLD were likely to be EBV+, CD20+, and more commonly involved the grafted organ.

13.2 PTLD and Epstein - Barr virus

Sara W. Dong, Barbra M. Blair, Carolyn D. Alonso. (2024). Single-Center Outcomes of Epstein–Barr Virus DNAemia in Adult Solid Organ Transplant Recipients, Journal of Transplantation, 2024, 5598324, 7 pages, 2024. https://doi.org/10.1155/2024/5598324

- A single-center retrospective review of adult solid organ transplant recipients with EBV DNAemia (whole blood EBV DNA PCR >200 copies/mL) between January 2015 and December 2019. Most of the 442 patients included were kidney (58%) and liver transplant recipients (31.9%) with intermediate EBV risk (97%). The overall incidence of EBV DNAemia in the cohort was 4.1% with a median time to detection of 14 months. Patients with an EBV serological mismatch (donor-positive, recipient-negative) had the highest proportion of DNAemia (37.5%). PTLD development was significantly associated with EBV DNAemia and occurred in 16.7% of patients with DNAemia and 0.7% of patients without EBV DNAemia. All patients with PTLD were managed with reduction in immunosuppression and rituximab.

Dierickx D, Pociupany M, Natkunam Y. (2022). Epstein-Barr virus-associated posttransplant lymphoproliferative disorders: new insights in pathogenesis, classification and treatment. Curr Opin Oncol. Sep 1;34(5):413-421. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35900750/

- A review of recent findings on pathogenesis, classification and treatment of EBV-positive PTLD. This review details the recent uptrend in EBV-directed therapies due to an improved understanding of PTLD mechanism and staging, and calls for refinement of the current WHO classification criteria.

Lau E, et al. (2021). Analysis of Post-Transplant Lymphoproliferative Disorder (PTLD) Outcomes with Epstein–Barr Virus (EBV) Assessments—A Single Tertiary Referral Center Experience and Review of Literature. Cancers. 13(4), 899. Retrieved from: https://www.mdpi.com/2072-6694/13/4/899

- Retrospective cohort study reporting the characteristics and outcomes of PTLD in the rituximab era with a total of 66 patients with PLTD following SOT at a median follow-up of 9 years. Overall median time from SOT to PTLD was 5.5 years with the longest time to diagnosis in infant transplants; overall survival was a median of 19 years. Response rate in the monomorphic DLBCL was 72% (n = 26) and 92% in polymorphic PTLD (n =12).

Allen UD, Preiksaitis JK. (2019). Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical Transplant. 33(9), e13652. Retrieved from: https://onlinelibrary.wiley.com/doi/abs/10.1111/ctr.13652.

- AST Infectious Disease Community of Practice updated guidelines. Reviews diagnosis, management and prevention of PTLD and EBV syndromes after solid organ transplantation.

13.3 PTLD following cardiac transplant

Kim IC, Kim SH, Youn JC, et al. (2024). Temporal Trends, Risk Factors, and Clinical Outcomes of De Novo Lymphoproliferative Disorders After Heart Transplantation. *JACC Heart Fail*. 2024;12(2):395-405. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38326002/

- A multicenter observational study of 28,136 heart transplant recipients focusing on the incidence, risk factors, and outcomes of PTLD. Data was obtained from the International Society for Heart and Lung Transplantation Thoracic (ISHLT) Organ Transplant Registry (TTX) from January 2000

to June 2015. Of the patients included in the study cohort, 1,069 (3.8%) developed PTLD within 10 years of transplantation. Risk factors for PTLD development within 3 years of transplantation in the study cohort include male sex, EBV primary mismatch (donor-positive, recipient negative), and transplant during earlier transplant era (between 2000-2007). Maintenance therapy at discharge from index admission with cyclosporine (vs. tacrolimus) was associated with a lower incidence of PTLD development. PTLD development within 3 years of transplantation was significantly associated with mortality.

Asleh R, Alnsasra H, Habermann TM, et al. (2022). Post-transplant Lymphoproliferative Disorder Following Cardiac Transplantation. Front Cardiovasc Med. Feb 23;9:787975. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8904724/

- A review of potential mechanisms underlying PTLD pathogenesis, as well as epidemiology, risk factors, prevention, treatment, and prognosis for PTLD; immunosuppression reduction, rituximab, and CHOP chemotherapy are listed as core pharmacotherapies, and the authors note that the role of mTOR inhibitors requires further research.

Bujo C, et al. (2021). Association between infectious event and de novo malignancy after heart transplantation. Heart Vessels. 36(4), 499-508. Retrieved from: https://link.springer.com/article/10.1007/s00380-020-01715-9

- Retrospective cohort study investigating the incidence of and risk factors for de novo malignancy after heart transplantation from a single center (Tokyo, Japan), with the correlation of infectious events and de novo malignancy. Further division of malignancy into PTLD group revealed the frequent negative EBV serostatus, CMV positive antigenemia, and occurrence of any viral or GI infections at ≤ 1 year.

13.4 PTLD following liver transplant

Zhang Y, Lv Y, Wang B, et al. (2023). Diagnosis and treatment of adult patients with PTLD at different sites after liver transplantation: A three-case report and literature review. Transpl Immunol. 2023;80:101881. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37392897/

- A case series and literature review of PTLD in liver transplant recipients. The patient cases described all had different initial PTLD sites and variable initial presentation. All patient cases were treated with immunosuppression reduction and antiviral therapy.

Janeela AM, Fouzia NA, Zachariah UG. (2024). Post-transplantation Lymphoproliferative Disorder (PTLD): In the Liver Transplant Recipient. *J Clin Exp Hepatol*. 2024;14(2):101286. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38076446/

- A comprehensive review of PTLD in the liver transplant recipient describing incidence, risk factors, immunosuppression, diagnosis, treatment, and prognosis.

Okamoto T, Okajima H, Uebayashi EY, et al. (2022). Management of Epstein-Barr Virus Infection and Post-Transplant Lymphoproliferative Disorder in Pediatric Liver Transplantation. J Clin Med. Apr 13;11(8):2166. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35456259/

- A review of PTLD pathogenesis, pathophysiology, diagnosis, treatment, and a single-center institutional experience. Authors describe the need for further research to investigate optimal immunosuppression after PTLD remission and to identify clinically relevant targets for pharmacotherapy.

Mucha K, Staros R, Foroncewicz B, et al. (2022). Comparison of Post-Transplantation Lymphoproliferative Disorder Risk and Prognostic Factors between Kidney and Liver Transplant Recipients. Cancers (Basel). Apr 13;14(8):1953. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9024969/

- A single-center retrospective review of 2598 kidney (KTR) and 1378 liver transplant recipients (LTR). 16 KTRs (0.62%) and 23 LTRs (1.67%) were diagnosed with PTLD, which developed earlier in LTRs, SOT patients over 45 years old, and patients receiving tacrolimus. Survival was longer in LTRs under 45 years old, and LTRs were more likely than KTRs to achieve complete remission. The authors recommend that KTRs and LTRs be evaluated separately in future studies due to stark differences affecting development and outcome of PTLD.

Éboli LPCB, Tannuri ACA, Tannuri U. (2022). Seropositivity for cytomegalovirus and PCR-EBV monitoring: Protective factors for posttransplant lymphoproliferative disorder in pediatric liver transplant. Pediatr Transplant. Jun;26(4):e14226. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35037358/

- A retrospective analysis of 428 pediatric liver transplant recipients, divided into patients with continuous PCR-EBV monitoring and patients without. Continuous PCR monitoring was evaluated for the impact of a change or reduction in immunosuppression on the number of viral copies. Results showed that seropositivity for CMV was an independent protective factor for PTLD and that monitoring the EBV viral load prevented the emergence of milder forms of PTLD.

Wang T, et al. (2021). Successful treatment of pediatric refractory Burkitt lymphoma PTLD after liver transplantation using anti-CD19 chimeric antigen receptor T-Cell therapy. Cell Transplant. 30, 1-8. Retrieved from: https://journals.sagepub.com/doi/full/10.1177/0963689721996649

- Case report of the first case of refractory BL-PTLD successfully treated using autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy. Sustained complete remission and manageable cytokine release syndrome were achieved.

13.5 PTLD following renal transplant

Ergisi M, Ooi B, Salim O, Papalois V. (2024). Post-transplant lymphoproliferative disorders following kidney transplantation: A literature review with updates on risk factors, prognostic indices, screening strategies, treatment and analysis of donor type [published correction appears in Transplant Rev (Orlando). 20204 Apr;38(2):100843]. *Transplant Rev (Orlando)*. 2024;38(2):100837. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38430887/

- A review of PTLD after kidney transplant focusing on risk factors, prognostic indices, screening strategies, treatment, and analysis of donor type. The authors describe an increased risk for PTLD in patients who received T-cell depleting therapy and differences in incidence of PTLD and time to PTLD development between donor groups.

Attieh RM, Wadei HM, Mao MA, et al. (2024). The impact of induction therapy on the risk of posttransplant lymphoproliferative disorder in adult kidney transplant recipients with donor-recipient serological Epstein-Barr virus mismatch. *Am J Transplant*. 2024 Aug;24(8):1486-1494. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38447887/

- A retrospective cohort study of 6,620 adult kidney transplant recipients using the Organ Procurement and Transplant Network (OPTN) database to assess the impact of induction therapy on the risk of PTLD in patients with EBV primary mismatch (donor-positive, recipient-negative) from January 2016 to December 2022. The patients in the study cohort were divided into groups based on the type of induction therapy they received including Rabbit antithymocyte globulin (ATG) or thymoglobulin (64%) basiliximab (23.4%), and alemtuzumab (12.6%). The overall incidence of PTLD over a median 2.9 year follow-up period was 2.5%. A multivariable analysis demonstrated that the risk of PTLD was significantly higher with ATG (p=0.002) and alemtuzumab (p=0.04) compared with basiliximab. Risk of PTLD was similar between ATG and alemtuzumab induction (p=0.61).

Chiodo Ortiz A, Petrossian G, Addonizio K, et al. (2023) Short-term decreased post transplant lymphoproliferative disorder risk after kidney transplantation using two novel regimens. Transpl Immunol. 2023 Feb;76:101774. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36528248/

- A single-center retrospective analysis of 354 adult kidney transplant recipients maintained on either low-doses of mycophenolate, tacrolimus and sirolimus, or low-doses of mycophenolate, tacrolimus and belatacept. No cases of PTLD were reported in either cohort. Both groups had similar rates of malignancy, mortality and CMV/BK viremia. Neither belatacept nor non-belatacept-based regimens posed an increased risk of early onset PTLD; both cohorts demonstrated low rates of rejection, malignancy, mortality, and graft failure

Franco A, Hernández D, Más-Serrano P, et al. (2022). Incidence of Lymphoproliferative Disorders After Renal Transplantation is Down, but the Poor Prognosis Remains. Multicenter 32-Year Cohort Study. Transplant Proc. Nov;54(9):2462-2466. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36379722/

- A retrospective review of 21,546 patients compared by decade of transplant and followed for at least 12 years. 331 patients (1.5%) developed PTLD, and incidence decreased significantly between decades. Most PTLD diagnoses were due to B-cell proliferation, and no classical risk factors were reported in 31.7% of affected patients. 1- and 5-year patient survival after diagnosis was 51% and 38%. Graft survival was 48% and 33%, and survival was stable. Authors concluded that PTLD incidence is low and decreasing, but prognosis remains poor.

Rouphael B, et al. (2016). Outcomes of kidney retransplantation in recipients with prior post-transplant lymphoproliferative disorder. Clin Transplant. 30(1), 60-5. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=26497471

- A retrospective review of 8 kidney transplant recipients who developed PTLD and subsequently underwent retransplantation from 1963 to December 2012 at a single U.S. center. After a median follow-up of 62.5 months (range 2-125 months) allograft survival was 87.5% (7 functioning grafts, 1 failed graft from chronic rejection), with no recurrence of PTLD. Three patients died from causes other than PTLD.

13.6 PTLD following intestinal transplant

Ionescu MI, Ip S, Barrett JK, Follows G, Butler AJ, Sharkey LM. (2024). Risk Factors Associated with PTLD Related Mortality in Adult Multivisceral Transplant Recipients - A Single Centre Cohort Study. *Chirurgia (Bucur)*. 2024;119(1):5-20. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38465712/

- A single-center, retrospective cohort study in adult multivisceral transplant recipients transplanted between 2013 and 2022 who developed PTLD. Among the study cohort (N=21), PTLD-associated mortality was 28%. Patients who had a splenectomy and those who required retransplantation had an increased relative risk of mortality. Other factors with a trend towards increased mortality include higher peak EBV load (p=0.0008), longer time from transplant to PTLD diagnosis (p=0.008), and higher donor age (p=0.001).

Stanley K, et al. (2018). Post-transplant lymphoproliferative disorder in pediatric intestinal transplant recipients: a literature review. Pediatr Transplant. 22(5), e13211. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29745058

- A comprehensive review of PTLD in pediatric intestinal transplant recipients in regard to pathology, presentation, and management. Also provides a summary of cases reviewed from the literature.

13.7 Management of PTLD

Khoury R, Grimley MS, Nelson AS, et al. (2024). Third-party virus specific T cells for the treatment of double stranded DNA viral reactivation and PTLD after solid organ transplant. Am J Transplant. 2024 Apr 19:S1600-6135(24)00280-6. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38643944/

- An open-label, phase 2 study of quadrivalent third party virus-specific T cell (VST) infusions in 98 solid organ transplant recipients for the treatment of BK polyomavirus (BKPyV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and adenovirus (ADV). Median patient age at time of first VST infusion was 47 years (range 10 months - 83 years). Most of the patients were kidney transplant recipients (53.1%), and the remaining patients were liver recipients (18.3%), heart recipients (16.3%), lung recipients (8.2%), or small bowel/multivisceral recipients (4.1%). An average of 2 VST infusions was given to each patient in the study. Infusions were well tolerated across organ groups with no infusion reactions reported. Three patients (3% total) experienced an episode of acute organ rejection within the first 4 weeks after the VST infusion, not considered directly related to the VST infusion by the authors. The overall response rate was 45% for BKPyV, 65% for CMV, 68% for ADV, and 61% for EBV. Of patients with PTLD, 20% had a complete response and 40% of patients had a partial response.

Puckerin R, Peters A. (2023). Rituximab monotherapy following surgical resection of gastrointestinal post-transplant lymphoproliferative disorder in solid organ transplant recipients. *Clin Transplant*. 2023;37(2):e14910. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36629389/

- A multicenter clinical study of 8 adult SOT recipients with newly diagnosed PTLD localized to the GI tract who were treated with surgical resection and rituximab monotherapy. The patients included were kidney (n=5), lung (n=2), and small bowel (n=1) transplant recipients diagnosed at a median of 4.2 years (range 0.2 - 19.3) post-transplant. PTLD subtypes were monomorphic diffuse large B cell lymphoma PTLD (n=5) and CD20+ polymorphic PTLD (n=3). PTLD involved the small intestine (n=5), large intestine (n=2), or both (n=1) and most patients (n=5) also had regional lymphadenopathy. Epstein–Barr virus–encoded small RNAs (EBER) in situ hybridization was positive in all patients except for one. Six patients required urgent surgical resection due to GI complications, while one patient under went planned surgical debulking and one patient required surgical excision to establish a diagnosis. Six patients had post-operative imaging which showed no evidence of residual lymphoma. Additional management included reduction of immunosuppression (n=5) and rituximab (n=5) once weekly for four weeks. Five-year progression-free survival (PFS) and overall survival were 67%. The authors concluded that the administration of rituximab monotherapy to prevent disease relapse after surgical resection of GI PTLD appears to be a viable treatment option.

Amengual JE, Pro B. (2023). How I treat posttransplant lymphoproliferative disorder. *Blood*. 2023;142(17):1426-1437. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37540819/

- A review of PTLD treatment in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT), including immunotherapy treatment options and a treatment approach for relapsed/refractory cases and for rare subtypes of PTLD. The author provides a treatment approach based on PTLD characteristics and includes a comprehensive assessment of available literature.

Atallah-Yunes SA, Salman O, Robertson MJ. (2023). Post-transplant lymphoproliferative disorder: Update on treatment and novel therapies. *Br J Haematol*. 2023;201(3):383-395. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36946218/

- An update on treatment of PTLD in SOT and hematopoietic stem cell transplant (HSCT) patients. This review focuses on less described/novel treatment options for PTLD such as aggressive chemotherapy, chimeric antigen receptor T-cell therapy, and immune checkpoint inhibitors.

Rubinstein J, Toner K, Gross T, et al. (2023). Diagnosis and management of post-transplant lymphoproliferative disease following solid organ transplantation in children, adolescents, and young adults. Best Pract Res Clin Haematol. Mar;36(1):101446. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36907642/

- A review of epidemiology, clinical presentation, pathologic classification, prevention, and management of PTLD. Current research and emerging therapies are described, including adoptive cellular therapy, antivirals, vaccines, monoclonal antibodies, checkpoint inhibitors, and small molecule inhibitors. Authors note a need to identify patients at high risk for aggressive disease, and ideal treatment regimens for refractory or relapsed PTLD.

Zaffiri L, Chambers ET. (2023). Screening and Management of PTLD. Transplantation. Mar 23. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36949032/

- A review summarizing available PTLD screening and treatment techniques to identify transplant recipients at high risk for PTLD development. Authors describes strengths and weaknesses of DNAemia monitoring and organ-specific factors, and state that screening and management has become progressively more standardized, resulting in improved outcomes. Future areas of research include minimization of toxicity and identification of safe and effective therapies for refractory or relapsing PTLD.

Portuguese AJ, Gauthier J, Tykodi SS, et al. (2023). CD19 CAR-T therapy in solid organ transplant recipients: case report and systematic review. Bone Marrow Transplant. Apr;58(4):353-359. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36575360/

- A case report of diffuse large B-cell lymphoma (DLBCL) PTLD treated with lisocabtagene maraleucel, and a systematic review of solid organ transplant recipients with PTLD treated with CD19 CAR-T therapy. The case patient achieved a complete response but relapsed 8 months later; this relapse was positive for CD19 despite CAR-T persistence. The systemic review identified 12 kidney, 2 liver, 2 heart, and 1 pancreas after kidney transplant recipients; 82.4% (14/17) responded to CAR-T therapy, with 58.5% (10/17) complete responses and a 6.5-month median response duration. Rejection occurred in 23.5% (4/17), with no graft failure. The authors state that CD19 CAR-T therapy offers short-term effectiveness and manageable toxicity in PTLD, although further investigation including more patients with prospective study design are suggested.

McKenna M, Epperla N, Ghobadi A, et al. (2023) Real-world evidence of the safety and survival with CD19 CAR-T cell therapy for relapsed/refractory solid organ transplant-related PTLD. Br J Haematol. Jul;202(2):248-255. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37129856/

- A multicenter retrospective analysis of 22 adults with relapsed/refractory SOT-associated PTLD treated with CD19 CAR-T cell therapy, including 14 kidney (64%), 3 liver (14%), 2 heart (9%), 1 intestinal (5%), 1 lung (5%), and 1 pancreas after kidney transplant (5%). 18 (82%) patients experienced cytokine release syndrome, and immune effector cell-associated neurotoxicity syndrome was observed in 16 (73%) patients. The overall response rate was 64% (55% complete). 3 patients (14%) experienced allograft rejection after CAR-T. Two-year progression-free and overall survival rates were 35% and 58%. Complete remission was associated with survival. CD19 CAR-T therapy in relapsed/refractory SOT-related PTLD appeared similar in safety and efficacy to established CAR-T data.

Styczynski J, Sadlok J, Styczynski T, et al. (2022). Management of Resistant Post-transplant Lymphoproliferative Disorder: CAR-T Is a New Option. Anticancer Res. Nov;42(11):5181-5186. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36288856/

- A review of chimeric antigen receptor-T cell (CART) therapy for resistant/refractory PTLD. This review describes anti-PD1 therapy, a new anti-CD20 agent, brentuximab vedotin, and zanubrutinib as known options for patients who failed first-line therapy, but notes that only individual successful cases have been identified. The authors describe real-world data of 17 patients treated with CAR-T for PTLD with a success rate of 76.5%, and 66-68% success rates for EBV-specific CTLs.

Wilkinson JD, Allen U, Green M, et al; IPTA Pediatric PTLD Consensus Guidelines Conference. (2022). The IPTA Nashville consensus conference on post-transplant lymphoproliferative disorders after solid

organ transplantation in children: I-Methodology for the development of consensus practice guidelines. Pediatr Transplant. Nov 11:e14333. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36369733/

- A report of methods used to produce evidence-based consensus guidelines on the definitions, diagnosis, prevention, and management of PTLD and related disorders after solid organ transplant in children.

Zimmermann H, Koenecke C, Dreyling MH, et al. (2022). Modified risk-stratified sequential treatment (subcutaneous rituximab with or without chemotherapy) in B-cell Post-transplant lymphoproliferative disorder (PTLD) after Solid organ transplantation (SOT): the prospective multicentre phase II PTLD-2 trial. Leukemia. Oct;36(10):2468-2478. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35974101/

- A prospective, multicenter, Phase II trial that tested modified risk-stratification in 60 adult SOT recipients with CD20-positive PTLD. Patients in full or partial remission after rituximab monotherapy then continued with rituximab; higher-risk patients received R-CHOP-21. Thoracic SOT recipients who progressed received alternating R-CHOP-21 and modified R-DHAOx. Rituximab was applied subcutaneously. Overall response was 45/48 (94%); treatment-related mortality was 4/59 (7%, 95% CI 2-17). Results with R-CHOP-21 in high-risk patients confirmed previous results, while new intensified immunochemotherapy in very-high-risk patients was disappointing.

Hernani R, Sancho A, Amat P, et al. (2021). CAR-T therapy in solid transplant recipients with post-transplant lymphoproliferative disease: case report and literature review. Curr Res Transl Med. Oct;69(4):103304. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34303899/

- A case report of successful use of axicabtagene ciloleucel to achieve complete response in one DLBCL PTLD patient after three relapses. and a review of limited published data. Use in SOT-related PTLD treated with CAR-T therapy.was associated with high efficacy and no severe toxicities. Authors note that most patients underwent dose decreases or discontinuation of immunosuppression, while only one case of rejection was documented noting this may be a feasible approach, although more research is needed to confirm this strategy. Authors also recommend multidisciplinary team evaluation of the use of CAR-T therapy, and that patients on lower doses of maintenance immunosuppression and without recent graft rejection are likely the best candidates.

Krishnamoorthy S, et al. (2021). CAR-T therapy in solid organ transplant recipients with treatment refractory posttransplant lymphoproliferative disorder. Am J Transplant. 21(2), 809-814. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/33089906/

- Case series reporting outcomes of three SOT patients (one heart, one kidney, one pancreas) with refractory PTLD that received CAR-T therapy. All patients had major complications from CAR-T therapy and eventually expired.

Jain MD, et al. (2020). Failure of rituximab is associated with a poor outcome in diffuse large B cell lymphoma-type post-transplant lymphoproliferative disorder. Br J Haematol. 189(1), 97-105. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32068243/

- Multicenter, retrospective study looking at patients (n=155) with DLBCL-type PTLD treated with regimens that included rituximab. Two-year overall survival with rituximab-containing therapy was 63.7% (95% CI 56.6 - 71.1%). No difference in survival between R-CHOP therapy and rituximab primary therapy. Multivariate analysis in 109 patients concluded that baseline IPI score and response to rituximab induction therapy are predictors for overall survival.

Trappe RU, et al. (2017). Response to rituximab induction is a predictive marker in B-cell post-transplant lymphoproliferative disorder and allows successful stratification into rituximab or R-CHOP consolidation in an international, prospective, multicenter phase II trial. J Clin Oncol. 35(5), 536-543. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=27992268

- Prospective, multicenter, open-label, phase II trial evaluating 152 CD20+ PTLD patients who failed reduced immunosuppression. All patients received rituximab whereby on day 50, if patients were complete responders they would continue rituximab monotherapy. All others would receive R-CHOP. The study concluded that treatment stratification into rituximab or R-CHOP consolidation on the basis of response to rituximab induction is safe and effective.

Trappe R, et al. (2012). Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicenter phase 2 PTLD-1 trial. Lancet Oncol. 13(2), 196-206. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/?term=22173060.

- International multicenter open-label phase 2 trial, treatment-naive adult solid-organ transplant recipients diagnosed with CD20-positive PTLD who had failed to respond to upfront immunosuppression reduction received four courses of rituximab (375 mg/m^2 IV) once a week followed by 4 weeks without treatment and four cycles of CHOP every 3 weeks. In case of disease progression during rituximab monotherapy, CHOP was started immediately. The primary endpoint was treatment efficacy measured as response rates in all patients who completed treatment with rituximab and CHOP, per protocol, and response duration, in all patients who completed all planned therapy and responded. Secondary endpoints were frequency of infections, treatment-related mortality, and overall survival.

Reshef R, et al. (2011). Reduction of immunosuppression as initial therapy for posttransplantation lymphoproliferative disorder. Am J Transplant. 11(2), 336-47. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/21219573.

- Retrospective review of solid organ recipients diagnosed with PTLD between August 1988 and June 2008 at a single U.S. center. Of 162 adult patients diagnosed, 148 were evaluated. Patients were treated with either reduced immunosuppression (RI) alone (n=67), surgical excision followed by RI (n=30), or other first line therapies with or without RI (n=51). The study demonstrated a 45% response rate from RI alone, with the majority being complete response. There was a 32% acute rejection rate with RI-containing regimens with some requiring a second transplant. Of note, monomorphic PTLD was diagnosed in 63% patients treated with RI alone vs. 39% patients treated with other first-line therapies, implying a selection of patients with monomorphic PTLD for treatment with RI alone (p=0.011). The study also identified the following risk factors for poor response: bulky disease, advanced stage, and older age.

Parker A, et al. (2010). Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients–BCSH and BTS Guidelines. Br J Haematol. 149(5), 693-705. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/20408848

- PTLD guidelines from a joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Hematology (BCSH) and the British Transplantation Society (BTS). This review details the therapeutic options recommended including reduction in immunosuppression, transplant organ resection, radiotherapy and chemotherapy.

Swinnen LJ, et al. (2008). Prospective study of sequential reduction in immunosuppression, interferon alpha-2B, and chemotherapy for posttransplantation lymphoproliferative disorder. Transplantation, 86(2), 215-22. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/18645482

- A multi-center, prospective, phase II study of 16 patients with biopsy-proven PTLD after any organ allograft (excluding lung) transplantation. A sequential approach was used in this study, starting with reduction in immunosuppression, escalating to interferon alpha2b, and finally to chemotherapy. The response rate to reduced immunosuppression was 0/16 complete remission and 1/16 (6%) partial remission. Six of the 16 patients (38%) had documented rejection during the period of reduced immunosuppression. Thirteen patients underwent treatment with IFN alpha with

2/13 (15%) complete remission and 2/13 (15%) partial remission. Lastly, 7 patients proceeded to ProMACE-CytaBOM chemotherapy with 67% complete remission.

Choquet S, et al. (2006). Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood. 107(8), 3053-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16254143

- Phase 2 study conducted at 15 French and 4 Belgian centers between May 2000 and December 2001. Forty-six patients with untreated B-PTLD that were not responding to tapering of immunosuppression were included and 43 patients (18 kidney, 11 heart, 7 liver, 4 lung, and 3 heart-lung) were analyzed. Treatment consisted of 4 weekly injections of rituximab at 375 mg/m^2. Immunosuppressive drugs were stopped if possible, or dosage reduced by at least 50% and/or the number of drugs reduced to no more than two. At day 80, 37 (86%) patients were alive and the response rate was 44.2%, including 12 patients with a complete response. The overall survival rate at 1 year was 67%.

Blaes AH, Peterson BA, Bartlett N, Dunn DL, Morrison VA. (2005). Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: results of a phase II trial. Cancer. 104(8):1661-7. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16149091

- Retrospective review of 11 transplant recipients (4 kidney, 1 heart, 1 kidney-pancreas, 4 single lung, and 1 bilateral lung) at two U.S. centers diagnosed with PTLD treated with rituximab. Immunosuppressive therapy was reduced in dose or discontinued in all patients at the discretion of the managing physician. Three patients received a course of acyclovir. The overall response rate was 64% (6 complete remission, 1 partial remission, 2 progressive disease, and 2 deaths) and 55% complete remission rate.

Jain AB, et al. (2005). Rituximab (chimeric anti-CD20 antibody) for posttransplant lymphoproliferative disorder after solid organ transplantation in adults: long-term experience from a single center. Transplant. 80(12), 1692-8. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16378063

- A report of a single U.S. center's utilization for rituximab in PTLD as salvage therapy on long term outcomes. The authors found poor response rates and survival rates compared to other studies. The patients in the analysis had a high tumor burden and did not receive surgical interventions prior to rituximab.

Oertel SH, et al. (2005). Effect of anti-CD 20 antibody rituximab in patients with posttransplant lymphoproliferative disorder (PTLD). Am J Transplant. 5(12), 2901-6. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/16303003

- A multi-center, prospective study investigated the use of rituximab in 17 patients with PTLD (5 heart, 4 kidney, 4 lung, and 4 liver) between 1999 and 2002. Patients were treated with four weekly doses of 375 mg/m^2 of rituximab. Immunosuppressive therapy was reduced in all patients prior to their entry into the study protocol. Complete remission was achieved in 9 patients (52.9%) with a mean duration of 17.8 months; interestingly, these 9 PTLD cases were EBV-associated. The mean overall survival period was 37.0 months with 11 patients still living at the time of publication.

Tsai DE, et al. (2001). Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation. 71(8), 1076-88. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/11374406.

- Retrospective review of 42 adult patients treated with either reduced immunosuppression (RI) with or without surgical resection of all known disease. 63% (19/30) responded to RI alone with multivariate analysis indicating elevated LDH, organ dysfunction, and multi-organ involvement as

risk factors for poor responders of RI. At the median follow-up of 147 weeks, 55% of patients were alive with 50% in complete remission.

13.8 Retransplantation following PTLD

Johnson SR, et al. (2006). Retransplantation after post-transplant lymphoproliferative disorders: an OPTN/UNOS database analysis. Am J Transplant. 6(11), 2743-9.
Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17049062

- The Organ Procurement and Transplant Network/United Network for Organ Sharing database was reviewed for individuals who developed PTLD and underwent retransplant from 1987 through 2004.